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PATENT
Attorney Docket No. **056291-5291**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
Dearg Sutherland BROWN, et al.	)	
	)	
Application No.: **10/581,305**	)	Group Art: **1615**
	)	
Filed: **June 1, 2006**	)	Examiner: *Unassigned*
	)	
For: **AMIDE DERIVATIVES BEARING A CYCLOPROPYLAMINOACARBONYL SUBSTITUENT USEFUL AS CYTOKINE INHIBITORS**	)	Date: **April 25, 2007**

Commissioner for Patents
U.S. Patent and Trademark Office
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Randolph Building
401 Dulany Street
Alexandria, VA 22314

Sir:

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

UNDER 37 C.F.R. § 1.97(b)

Pursuant to 37 C.F.R. §§ 1.56 and 1.97(b), Applicants request the Examiner to consider this Supplemental Information Disclosure Statement and the documents listed on the attached Form PTO-1449. To the best of the undersigned's knowledge, this Supplemental Information Disclosure Statement is being filed before the mailing date of a first Office Action on the merits for the above-referenced application. Accordingly, Applicants do not believe a fee is due for filing this Supplemental Information Disclosure Statement.

A copy of the listed document is attached. Applicants respectfully request that the Examiner initial and return the Form PTO-1449, indicating that the information has been considered and made of record herein.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /R.C./

This submission does not represent that a search has been made or that no better art exists and does not constitute an admission that each or all of the listed documents are material or constitute "prior art." Applicants reserve the right to take appropriate action to establish the patentability of the disclosed invention over the listed documents, should one or more of the documents be applied against the claims of the present application.

Except for issue fees payable under 37 C.F.R. §1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account No. 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,
Morgan Lewis & Bockius LLP

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	Applicants: **Dearg Sutherland BROWN** *et al.*	
	Filing Date: **June 1, 2006**	Group Art Unit: *Unassigned*

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U.S. PATENT DOCUMENTS

Initial		Document No.	Date	Name	Class	Sub-Class	Filing Date

FOREIGN PATENT DOCUMENTS

		Document No.	Date	Country	Class	Sub-Class	Translation
	1.	WO 2005/042502	May 12, 2005	WIPO			

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, etc.)

Examiner /Raymond Covington/ au 1625	Date Considered 12/16/09

Examiner: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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WO2005042502

Publication Title:

AMIDE DERIVATIVES

Abstract:

Abstract of WO2005042502

The invention concerns a compound of the Formula (I) wherein m is 0-2 and each R<1> is a group such as hydroxy, halogeno, trifluoromethyl heterocyclyl and heterocyclyloxy; R<2> is halogeno, trifluoromethyl or (1-6C)alkyl; R<3> is hydrogen, halogeno or (1-6C)alkyl; and R<4> is (3-6C)cycloalkyl;or pharmaceutically-acceptable salts thereof; processes for their preparation, pharmaceutical compositions containing them and their use in the treatment of diseases or medical condions mediated by cytokines. Data supplied from the esp@cenet database - Worldwide

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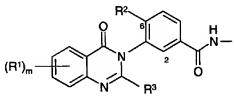
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: AMIDE DERIVATIVES



(I)

(57) Abstract: The invention concerns a compound of the Formula (I) wherein m is 0-2 and each R^1 is a group such as hydroxy, halogeno, trifluoromethyl heterocyclyl and heterocyclyloxy; R^2 is halogeno, trifluoromethyl or (1-6C)alkyl; R^3 is hydrogen, halogeno or (1-6C)alkyl; and R^4 is (3-6C)cycloalkyl;or pharmaceutically-acceptable salts thereof; processes for their preparation, pharmaceutical compositions containing them and their use in the treatment of diseases or medical condions mediated by cytokines.

WO 2005/042502 A1

AMIDE DERIVATIVES

This invention relates to amide derivatives, or pharmaceutically-acceptable salts thereof which are useful as inhibitors of cytokine mediated disease. The invention also relates to processes for the manufacture of said amide derivatives, to pharmaceutical compositions containing said amide derivatives and to their use in therapeutic methods, for example by virtue of inhibition of cytokine mediated disease.

The amide derivatives disclosed in the present invention are inhibitors of the production of cytokines such as Tumour Necrosis Factor (hereinafter TNF), for example TNFα, and various members of the interleukin (hereinafter IL) family, for example IL-1, IL-6 and IL-8. Accordingly the amide derivatives of the invention will be useful in the treatment of diseases or medical conditions in which excessive production of cytokines occurs, for example excessive production of TNFα or IL-1. It is known that cytokines are produced by a wide variety of cells such as monocytes and macrophages and that they give rise to a variety of physiological effects which are believed to be important in disease or medical conditions such as inflammation and immunoregulation. For example, TNFα and IL-1 have been implicated in the cell signalling cascade which is believed to contribute to the pathology of disease states such as inflammatory and allergic diseases and cytokine-induced toxicity. It is also known that, in certain cellular systems, TNFα production precedes and mediates the production of other cytokines such as IL-1.

Abnormal levels of cytokines have also been implicated in, for example, the production of physiologically-active eicosanoids such as the prostaglandins and leukotrienes, the stimulation of the release of proteolytic enzymes such as collagenase, the activation of the immune system, for example by stimulation of T-helper cells, the activation of osteoclast activity leading to the resorption of calcium, the stimulation of the release of proteoglycans from, for example, cartilage, the stimulation of cell proliferation and to angiogenesis.

Cytokines are also believed to be implicated in the production and development of disease states such as inflammatory and allergic diseases, for example inflammation of the joints (especially rheumatoid arthritis, osteoarthritis and gout), inflammation of the gastrointestinal tract (especially inflammatory bowel disease, ulcerative colitis, Crohn's disease and gastritis), skin disease (especially psoriasis, eczema and dermatitis) and respiratory disease (especially asthma, bronchitis, allergic rhinitis, chronic obstructive

pulmonary disease and adult respiratory distress syndrome), and in the production and development of various cardiovascular and cerebrovascular disorders such as congestive heart failure, acute heart failure, myocardial infarction, the formation of atherosclerotic plaques, hypertension, platelet aggregation, angina, stroke, reperfusion injury, vascular injury including restenosis and peripheral vascular disease, and, for example, various disorders of bone metabolism such as osteoporosis (including senile and postmenopausal osteoporosis), Paget's disease, bone metastases, hypercalcaemia, hyperparathyroidism, osteosclerosis, osteoperosis and periodontitis, and the abnormal changes in bone metabolism which may accompany rheumatoid arthritis and osteoarthritis. Excessive cytokine production has also been implicated in mediating certain complications of bacterial, fungal and/or viral infections such as endotoxic shock, septic shock and toxic shock syndrome and in mediating certain complications of CNS surgery or injury such as neurotrauma and ischaemic stroke. Excessive cytokine production has also been implicated in mediating or exacerbating the development of diseases involving cartilage or muscle resorption, pulmonary fibrosis, cirrhosis, renal fibrosis, the cachexia found in certain chronic diseases such as malignant disease and acquired immune deficiency syndrome (AIDS), chronic obstructive pulmonary disease, tumour invasiveness and tumour metastasis and multiple sclerosis. Excessive cytokine production has also been implicated in pain.

Evidence of the central role played by TNFα in the cell signalling cascade which gives rise to rheumatoid arthritis is provided by the efficacy in clinical studies of antibodies of TNFα (The Lancet, 1994, 344, 1125 and British Journal of Rheumatology, 1995, 34, 334).

Thus cytokines such as TNFα and IL-1 are believed to be important mediators of a considerable range of diseases and medical conditions. Accordingly it is expected that inhibition of the production of and/or effects of these cytokines will be of benefit in the prophylaxis, control or treatment of such diseases and medical conditions.

Without wishing to imply that the amide derivatives disclosed in the present invention possesses pharmacological activity only by virtue of an effect on a single biological process, it is believed that the amide derivatives inhibit the effects of cytokines by virtue of inhibition of the enzyme p38 kinase. p38 kinase, otherwise known as cytokine suppressive binding protein (hereinafter CSBP) and reactivating kinase (hereinafter RK), is a member of the mitogen-activated protein (hereinafter MAP) kinase family of enzymes which is known to be activated by physiological stress such as that induced by ionising radiation, cytotoxic agents, and toxins,

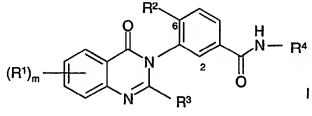
for example endotoxins such as bacterial lipopolysaccharide, and by a variety of agents such as the cytokines, for example TNFα and IL-1. It is known that p38 kinase phosphorylates certain intracellular proteins which are involved in the cascade of enzymatic steps which leads to the biosynthesis and excretion of cytokines such as TNFα and IL-1. Known inhibitors of p38 kinase have been reviewed by G. J. Hanson in Expert Opinions on Therapeutic Patents, 1997, 7, 729-733. p38 kinase is known to exist in isoforms identified as p38α and p38β.

The amide derivatives disclosed in the present invention are inhibitors of the production of cytokines such as TNF, in particular of TNFα, and various interleukins, in particular IL-1.

It is known from the International Patent Application WO 00/55153, that certain benzamide derivatives are inhibitors of the production of cytokines such as TNF, and various interleukins. One of the disclosed compounds is 3-[5-(2-chloropyrid-4-ylcarbonylamino)-2-methylphenyl]-6-(4-methylpiperazin-1-yl)-3,4-dihydroquinazolin-4-one(Comparator Compound A). Another of the disclosed compounds is 3-[5-(3,5-difluorobenzamido)-2-methylphenyl]-6-(4-methylpiperazin-1-yl)-3,4-dihydroquinazolin-4-one (Comparator Compound B).

There is no disclosure in this document of an amide derivative which bears a (3-6C)cycloalkylaminocarbonyl substituent at the 3-position of the central 6-methylphenyl core. We have now found that such compounds possess potent cytokine inhibitory activity and have desirable pharmacological activity profiles.

According to the first aspect of present invention there is provided a compound of the Formula I



I

wherein m is 0, 1 or 2;

R^1 is halogeno, hydroxy, cyano, trifluoromethyl, trifluoromethoxy, (1-6C)alkyl, (1-6C)alkoxy, (2-6C)alkenyl, (2-6C)alkynyl, (2-6C)alkanoyl, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, hydroxy-(2-6C)alkoxy, amino-(2-6C)alkoxy, cyano-(2-6C)alkoxy, (1-6C)alkylamino-(2-6C)alkoxy, di-[(1-6C)alkyl]amino-(2-6C)alkoxy, (1-6C)alkoxy-

(2-6C)alkoxy, carbamoyl-(1-6C)alkoxy, N-(1-6C)alkylcarbamoyl-(1-6C)alkoxy, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di[(1-6C)alkyl]amino-(1-6C)alkyl, carbamoyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl-(1-6C)alkyl, hydroxy-(2-6C)alkylamino, cyano-(2-6C)alkylamino, halogeno-(2-6C)alkylamino, amino-(2-6C)alkylamino, (1-6C)alkoxy-(2-6C)alkylamino, (1-6C)alkylamino-(2-6C)alkylamino, di-[(1-6C)alkyl]amino-(2-6C)alkylamino, heteroaryl, heteroaryl-(1-6C)alkyl, heteroaryloxy, heteroaryl-(1-6C)alkoxy, heteroarylamino, heterocyclyl, heterocyclyl-(1-6C)alkyl, heterocyclyloxy, heterocyclyl-(1-6C)alkoxy and heterocyclylamino,

and wherein any aryl, heteroaryl or heterocyclyl group in a R^1 substituent may optionally bear 1 or 2 substituents selected from hydroxy, halogeno, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl-(1-6C)alkyl, (3-6C)cycloalkyl-(1-6C)alkoxy, (1-6C)alkoxy, carboxy, (1-6C)alkoxycarbonyl, (1-6C)alkoxycarbonyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, carboxy-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl,

and wherein any of the R^1 substituents defined hereinbefore which comprises a CH_2 group which is attached to 2 carbon atoms or a CH_3 group which is attached to a carbon or nitrogen atom may optionally bear on each said CH_2 or CH_3 group one or more substituents selected from halogeno, hydroxy, amino, trifluoromethyl, trifluoromethoxy, oxo, carboxy, carbamoyl, acetamido, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (3-6C)cycloalkyl, (3-6C)cycloalkoxy, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, halogeno-(1-6C)alkyl, (1-6C)alkoxy-(2-6C)alkoxy, (1-6C)alkoxycarbonyl, carbamoyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (1-6C)sulphonyl, (1-6C)sulphamoyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl and heterocyclyloxy, and wherein any heterocyclyl group in a R^1 substituent may optionally bear 1 or 2 oxo or thioxo substituents;

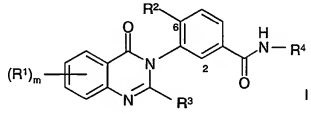
R^2 is halogeno, trifluoromethyl or (1-6C)alkyl;

R^3 is hydrogen, halogeno or (1-6C)alkyl; and

R^4 is (3-6C)cycloalkyl, and R^4 may be optionally substituted by one or more substituents selected from halogeno, hydroxy, amino, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino;

or a pharmaceutically-acceptable salt thereof.

According to another aspect of the present invention there is provided a compound of the Formula I



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wherein m is 0, 1 or 2;

R^1 is amino-(2-6C)alkoxy, (1-6C)alkylamino-(2-6C)alkoxy, di-[(1-6C)alkyl]amino-(2-6C)alkoxy, amino-(2-6C)alkylamino, (1-6C)alkylamino-(2-6C)alkylamino, di-[(1-6C)alkyl]amino-(2-6C)alkylamino, aryl, aryl-(1-6C)alkyl, aryl-(1-6C)alkoxy, aryloxy, arylamino, heteroaryl, heteroaryl-(1-6C)alkyl, heteroaryloxy, heteroaryl-(1-6C)alkoxy, heteroarylamino, heterocyclyl, heterocyclyl-(1-6C)alkyl, heterocyclyloxy, heterocyclyl-(1-6C)alkoxy or heterocyclylamino,

and wherein any aryl, heteroaryl or heterocyclyl group in a R^1 substituent may optionally bear 1 or 2 substituents selected from hydroxy, halogeno, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl-(1-6C)alkyl, (3-6C)cycloalkyl-(1-6C)alkoxy, (1-6C)alkoxy, carboxy, (1-6C)alkoxycarbonyl, (1-6C)alkoxycarbonyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, carboxy-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl,

and wherein any of the R^1 substituents defined hereinbefore which comprises a CH_2 group which is attached to 2 carbon atoms or a CH_3 group which is attached to a carbon atom may optionally bear on each said CH_2 or CH_3 group one or more substituents selected from hydroxy, amino, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino,

and wherein any heterocyclyl group in a R^1 substituent may optionally bear 1 or 2 oxo or thioxo substituents;

R^2 is halogeno, trifluoromethyl or (1-6C)alkyl;

R^3 is hydrogen, halogeno or (1-6C)alkyl; and

R^4 is (3-6C)cycloalkyl, and R^4 may be optionally substituted by one or more substituents selected from halogeno, hydroxy, amino, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino;
or a pharmaceutically-acceptable salt thereof.

In this specification, the term (1-6C)alkyl includes straight-chain and branched-chain alkyl groups such as propyl, isopropyl and tert-butyl. References to individual alkyl groups such as "propyl" are specific for the straight-chain version only, references to individual branched-chain alkyl groups such as "isopropyl" are specific for the branched-chain version only. In this specification, the term (3-6C)cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, and cyclohexyl. References to individual cycloalkyl groups such as "cyclopentyl" are specific for that 5-membered ring only.

It is to be understood that, insofar as certain of the compounds of Formula I defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the property of inhibiting cytokines, in particular TNF. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, inhibitory properties against TNF may be evaluated using the standard laboratory techniques referred to hereinafter.

Suitable values for the generic radicals referred to above include those set out below.

A suitable value for R^1 when it is aryl is, for example, phenyl, indenyl, indanyl, naphthyl, tetrahydronaphthyl or fluorenyl, preferably phenyl.

A suitable value for R^1 when it is heteroaryl is, for example, an aromatic 5- or 6-membered monocyclic ring, a 9- or 10-membered bicyclic ring or a 13- or 14-membered tricyclic ring each with up to five ring heteroatoms selected from oxygen, nitrogen and sulphur, for example furyl, pyrrolyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazenyl, benzofuranyl, indolyl, benzothienyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, indazolyl, benzofurazanyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, carbazolyl, dibenzofuranyl, dibenzothiophenyl, S,S-dioxodibenzothiophenyl, xanthenyl, dibenzo-1,4-dioxinyl, phenoxathiinyl, phenoxazinyl, dibenzothiinyl, phenothiazinyl, thianthrenyl, benzofuropyridyl,

pyridoindolyl, acridinyl or phenanthridinyl, preferably furyl, thienyl, oxazolyl, isoxazolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, benzofuranyl, indolyl, benzothienyl, benzoxazolyl, benzimidazolyl, benzothiazolyl, indazolyl, benzofurazanyl, quinolyl, isoquinolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, carbazolyl, dibenzofuranyl, dibenzothiophenyl or xanthenyl, more preferably furyl, thienyl, isoxazolyl, thiazolyl, pyridyl, benzothienyl, benzofurazanyl, quinolyl, carbazolyl, dibenzofuranyl or dibenzothiophenyl.

A suitable value for R^1 when it is heterocyclyl is, for example, a non-aromatic saturated or partially saturated 3- to 10-membered monocyclic or bicyclic ring or a 5- to 7-membered monocyclic ring each with up to five heteroatoms selected from oxygen, nitrogen and sulphur, for example oxiranyl, oxetanyl, azetidinyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolinyl, pyrrolidinyl, imidazolinyl, imidazolidinyl, pyrazolinyl, pyrazolidinyl, 1,1-dioxidoisothiazolidinyl, morpholinyl, thiomorpholinyl, tetrahydro-1,4-thiazinyl, 1,1-dioxotetrahydro-1,4-thiazinyl, piperidinyl, homopiperidinyl, piperazinyl, homopiperazinyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyrimidinyl or tetrahydropyrimidinyl or benzo derivatives thereof such as 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzothienyl, indolinyl, isoindolinyl, chromanyl and isochromanyl, preferably azetidin-1-yl, 3-pyrrolin-1-yl, pyrrolidin-1-yl, pyrrolidin-2-yl, 1,1-dioxidoisothiazolidin-2-yl, morpholino, 1,1-dioxotetrahydro-4H-1,4-thiazin-4-yl, piperidin-3-yl, piperidin-4-yl, homopiperidin-1-yl, piperidino, piperazin-1-yl or homopiperazin-1-yl. A suitable value for such a group which bears 1 or 2 oxo or thioxo substituents is, for example, 2-oxopyrrolidinyl, 2-thioxopyrrolidinyl, 2-oxoimidazolidinyl, 2-thioxoimidazolidinyl, 2-oxopiperidinyl, 2,5-dioxopyrrolidinyl, 2,5-dioxoimidazolidinyl or 2,6-dioxopiperidinyl.

A suitable value for R^4 or R^1 when it is (3-6C)cycloalkyl, or for a substituent within R^1 when it is (3-6C)cycloalkyl is, for example, a saturated monocyclic 3- to 6-membered carbon ring such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, preferably cyclopropyl, cyclopentyl or cyclobutyl, more preferably cyclopropyl.

A suitable value for a substituent within R^1 when it is (3-6C)cycloalkyl-(1-6C)alkyl is, for example, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, cyclopropylethyl , preferably cyclopropylmethyl or cyclopropylethyl, more preferably cyclopropylmethyl.

Suitable values for various R^1, R^2 or R^3 groups, or for various substituents on R^1 or on an aryl, heteroaryl or heterocyclyl group within R^1 include:-

for halogeno:	fluoro, chloro, bromo and iodo;
for (1-6C)alkyl:	methyl, ethyl, propyl, isopropyl and tert-butyl;
for (2-6C)alkenyl:	vinyl and allyl;
for (2-6C)alkynyl:	ethynyl and 2-propynyl;
for (1-6C)alkoxy:	methoxy, ethoxy, propoxy, isopropoxy and butoxy;
for (1-6C)alkylthio:	methylthio, ethylthio and propylthio;
for (1-6C)alkylsulphinyl:	methylsulphinyl, ethylsulphinyl and propylsulphinyl;
for (1-6C)alkylsulphonyl:	methylsulphonyl, ethylsulphonyl and propylsulphonyl;
for hydroxy-(2-6C)alkoxy:	2-hydroxyethoxy, 3-hydroxypropoxy, 2-hydroxy-1-methylethoxy,2-hydroxy-2-propoxy and 4-hydroxybutoxy;
for cyano-(1-6C)alkoxy:	cyanomethoxy, 2-cyanoethoxy and 3-cyanopropoxy;
for (1-6C)alkoxy-(2-6C)alkoxy:	2-methoxyethoxy, 2-ethoxyethoxy, 3-methoxypropoxy, 2-methoxy-1-methylethoxy and 4-ethoxybutoxy;
for carbamoyl-(1-6C)alkoxy:	carbamoylmethoxy and 2-carbamoylethoxy;
for N-(1-6C)alkylcarbamoyl-(1-6C)alkoxy:	N-methylcarbamoylmethoxy, 2-(N-ethylcarbamoyl)ethoxy and 3-(N-methylcarbamoyl)propoxy;
for (3-6C)cycloalkyl-(1-6C)alkyl	(3-6C)cycloalkylmethyl and (3-6C)cycloalkylethyl;
for (1-6C)alkylamino:	methylamino, ethylamino and propylamino;
for di-[(1-6C)alkyl]amino:	dimethylamino, diethylamino and N-ethyl-N-methylamino;
for (1-6C)alkoxycarbonyl:	methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and tert-butoxycarbonyl;
for N-(1-6C)alkylcarbamoyl:	N-methylcarbamoyl, N-ethylcarbamoyl and N-propylcarbamoyl;
for N,N-di-[(1-6C)alkyl]carbamoyl:	N,N-dimethylcarbamoyl, N-ethyl-N-methylcarbamoyl and N,N-diethylcarbamoyl;
for (2-6C)alkanoyl:	acetyl and propionyl;

for halogeno-(1-6C)alkyl: fluoromethyl, chloromethyl, bromomethyl, difluoromethyl, dichloromethyl, dibromomethyl, 2-fluoroethyl, 2-chloroethyl and 2-bromoethyl;

for hydroxy-(1-6C)alkyl: hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl and 3-hydroxypropyl;

for carbamoyl-(1-6C)alkyl: carbamoylmethyl, 1-carbamoylethyl, 2-carbamoylethyl and 3-carbamoylpropyl;

for N-(1-6C)alkylcarbamoyl-(1-6C)alkyl: N-methylcarbamoylmethyl, N-ethylcarbamoylmethyl, N-propylcarbamoylmethyl, 1-(N-methylcarbamoyl)ethyl, 1-(N-ethylcarbamoyl)ethyl, 2-(N-methylcarbamoyl)ethyl, 2-(N-ethylcarbamoyl)ethyl and 3-(N-methylcarbamoyl)propyl;

for (1-6C)alkoxy-(1-6C)alkyl: methoxymethyl, ethoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 2-ethoxyethyl and 3-methoxypropyl;

for amino-(1-6C)alkyl: aminomethyl, 2-aminoethyl, 1-aminoethyl and 3-aminopropyl;

for carboxy-(1-6C)alkyl: carboxymethyl, 1-carboxyethyl, 2-carboxyethyl, 3-carboxypropyl and 4-carboxybutyl;

for cyano-(1-6C)alkyl: cyanomethyl, 2-cyanoethyl, 1-cyanoethyl and 3-cyanopropyl;

for (1-6C)alkylamino-(1-6C)alkyl: methylaminomethyl, ethylaminomethyl, 1-methylaminoethyl, 2-methylaminoethyl, 2-ethylaminoethyl and 3-methylaminopropyl;

for di-[(1-6C)alkyl]amino-(1-6C)alkyl: dimethylaminomethyl, diethylaminomethyl, 1-dimethylaminoethyl, 2-dimethylaminoethyl and 3-dimethylaminopropyl.

for amino-(2-6C)alkoxy: 2-aminoethoxy, 2-amino-1-methylethoxy, 3-aminopropoxy, 2-amino-2-methylpropoxy and 4-aminobutoxy;

for (1-6C)alkylamino-(2-6C)alkoxy: 2-methylaminoethoxy, 2-methylamino-1-methylethoxy, and

3-ethylaminopropoxy,

for di-[(1-6C)alkyl]amino-(2-6C)alkoxy: 2-dimethylaminoethoxy, 2-diethylaminoethoxy, 2-dimethylaminopropoxy, 2-dimethylamino-2-methylethoxy, 3-dimethylaminopropoxy and 4-dimethylaminobutoxy, 2-(N-methyl-N-isopropylamino)ethoxy, and 2-(N-ethyl-N-isopropylamino)ethoxy;

for amino-(2-6C)alkylamino: 2-aminoethylamino, 3-aminopropylamino, 2-amino-2-methylpropylamino and 4-aminobutylamino;

for halogeno-(2-6C)alkylamino: 2-fluoroethylamino, 2-chloroethylamino, 2-bromoethylamino, 3-fluoropropylamino and 3-chloropropylamino;

for hydroxy-(2-6C)alkylamino: 2-hydroxyethylamino, 3-hydroxypropylamino, 2-hydroxy-2-methylpropylamino and 4-hydroxybutylamino;

for cyano-(1-6C)alkylamino: cyanomethylamino, 2-cyanoethylamino and 3-cyanopropylamino;

for (1-6C)alkoxy-(2-6C)alkylamino: 2-methoxyethylamino, 2-ethoxyethylamino, 3-methoxypropylamino and 3-ethoxypropylamino;

for (1-6C)alkylamino-(2-6C)alkylamino: 2-methylaminoethylamino, 2-ethylaminoethylamino, 2-propylaminoethylamino, 3-methylaminopropylamino, 3-ethylaminopropylamino, 2-methylamino-2-methylpropylamino and 4-methylaminobutylamino;

for di-[(1-6C)alkyl]amino-(2-6C)alkylamino: 2-dimethylaminoethylamino, 2-(N-ethyl-N-methylamino)ethylamino, 2-diethylaminoethylamino, 2-dipropylaminoethylamino, 3-dimethylaminopropylamino, 3-diethylaminopropylamino, 2-dimethylamino-2-methylpropylamino and 4-dimethylaminobutylamino;

Suitable values for R^1 and suitable values for a substituent on R^1 or R^4 include:-

for aryl-(1-6C)alkyl:	benzyl, 2-phenylethyl, 2-phenylpropyl and 3-phenylpropyl;
for aryl-(1-6C)alkoxy:	benzyloxy and 2-phenylethoxy;
for aryloxy:	phenoxy and 2-naphthyloxy;
for arylamino:	anilino;
for heteroaryl-(1-6C)alkyl:	heteroarylmethyl, heteroarylethyl, 2-heteroarylethyl, 2-heteroarylpropyl and 3-heteroarylpropyl;
for heteroaryl-(1-6C)alkoxy:	heteroarylmethoxy and 2-heteroarylethoxy;
for heterocyclyl-(1-6C)alkyl:	heterocyclylmethyl, 2-heterocyclylethyl, 2-heterocyclylpropyl and 3-heterocyclylpropyl;
for heterocyclyl-(1-6C)alkoxy:	heterocyclylmethoxy and 2-heterocyclylethoxy;
for (2-6C)alkanoyloxy:	acetoxy and propionyloxy:
for (1-6C)alkanoylamino:	formamido, acetamido and propionamido;
for (1-6C)alkoxycarbonyl-(1-6C)alkyl:	methoxycarbonylmethyl, ethoxycarbonylmethyl, tert-butoxycarbonylmethyl, 1-methoxycarbonylethyl, 1-ethoxycarbonylethyl, 2-methoxycarbonylethyl, 2-ethoxycarbonylethyl, 3-methoxycarbonylpropyl and 3-ethoxycarbonylpropyl;

A suitable pharmaceutically-acceptable salt of a compound of the Formula I, for example, an acid-addition salt of a compound of the Formula I which is sufficiently basic, for example, an acid-addition salt with an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric, maleic, tartaric, fumaric, hemifumaric, succinic, hemisuccinic, mandelic, methanesulphonic, dimethanesulphonic, ethane-1,2-sulphonic, benzenesulphonic, salicylic or 4-toluenesulphonic acid.

Further values of m, R^1, R^2, R^3 and R^4 are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

m is 0, 1 or 2.

m is 1 or 2.

m is 1.

m is 2.

R^1 is halogeno, hydroxy, cyano, trifluoromethyl, trifluoromethoxy, (1-6C)alkyl, (1-6C)alkoxy, (2-6C)alkenyl, (2-6C)alkynyl, (2-6C)alkanoyl, (1-6C)alkylthio, (1-6C)alkylsulphonyl, hydroxy-(2-6C)alkoxy, amino-(2-6C)alkoxy, cyano-(2-6C)alkoxy, (1-6C)alkylamino-(2-6C)alkoxy, di-[(1-6C)alkyl]amino-(2-6C)alkoxy, (1-6C)alkoxy-(2-6C)alkoxy, di[(1-6C)alkyl]amino-(1-6C)alkyl, carbamoyl-(1-6C)alkyl, heteroaryl-(1-6C)alkyl, heteroaryl-(1-6C)alkoxy, heterocyclyl, heterocyclyl-(1-6C)alkyl, heterocyclyloxy and heterocyclyl-(1-6C)alkoxy,

and wherein any heteroaryl or heterocyclyl group in a R^1 substituent may optionally bear 1 or 2 substituents selected from hydroxy, halogeno, (1-6C)alkyl, (3-6C)cycloalkyl-(1-6C)alkyl, (3-6C)cycloalkyl-(1-6C)alkoxy, (1-6C)alkoxy, (1-6C)alkoxycarbonyl, (1-6C)alkoxycarbonyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl,

and wherein any of the R^1 substituents defined hereinbefore which comprises a CH_2 group which is attached to 2 carbon atoms or a CH_3 group which is attached to a carbon or nitrogen atom may optionally bear on each said CH_2 or CH_3 group one or more substituents selected from halogeno, hydroxy, trifluoromethyl, oxo (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (3-6C)cycloalkyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, halogeno-(1-6C)alkyl, (1-6C)alkoxycarbonyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl and heterocyclyloxy,

and wherein any heterocyclyl group in a R^1 substituent may optionally bear 1 or 2 oxo or thioxo substituents.

R^1 is halogeno, hydroxy, (1-6C)alkoxy, (2-6C)alkenyl, (2-6C)alkynyl, (2-6C)alkanoyl, (1-6C)alkylthio, (1-6C)alkylsulphonyl, amino-(2-6C)alkoxy, (1-6C)alkylamino-(2-6C)alkoxy, di-[(1-6C)alkyl]amino-(2-6C)alkoxy, di[(1-6C)alkyl]amino-(1-6C)alkyl, carbamoyl-(1-6C)alkyl, heteroaryl-(1-6C)alkyl, heterocyclyl, heterocyclyloxy and heterocyclyl-(1-6C)alkoxy,

and wherein any heteroaryl or heterocyclyl group in a R^1 substituent may optionally bear 1 or 2 substituents selected from hydroxy, halogeno, (1-6C)alkyl, (3-6C)cycloalkyl-(1-6C)alkyl, (3-6C)cycloalkyl-(1-6C)alkoxy, (1-6C)alkoxy, (1-6C)alkoxycarbonyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl,

and wherein any of the R^1 substituents defined hereinbefore which comprises a CH_2 group which is attached to 2 carbon atoms or a CH_3 group which is attached to a carbon or nitrogen atom may optionally bear on each said CH_2 or CH_3 group one or more substituents selected from halogeno, hydroxy, trifluoromethyl, (1-6C)alkyl, (3-6C)cycloalkyl, (1-6C)alkoxy, di-[(1-6C)alkyl]amino, (1-6C)alkoxy-(1-6C)alkyl, (1-6C)alkoxycarbonyl, heteroaryl-(1-6C)alkyl, heterocyclyl and heterocyclyloxy.

R^1 is halogeno, hydroxy, (1-6C)alkoxy, (2-6C)alkenyl, (2-6C)alkynyl, (2-6C)alkanoyl, (1-6C)alkylthio, (1-6C)alkylsulphonyl, amino-(2-6C)alkoxy, (1-6C)alkylamino-(2-6C)alkoxy, di-[(1-6C)alkyl]amino-(2-6C)alkoxy, di[(1-6C)alkyl]amino-(1-6C)alkyl, carbamoyl-(1-6C)alkyl, heteroaryl-(1-6C)alkyl, heterocyclyl, heterocyclyloxy and heterocyclyl-(1-6C)alkoxy,

and wherein any heteroaryl or heterocyclyl group in a R^1 substituent may optionally bear 1 or 2 substituents selected from hydroxy, halogeno, (1-6C)alkyl, (3-6C)cycloalkyl-(1-6C)alkyl, (3-6C)cycloalkyl-(1-6C)alkoxy, (1-6C)alkoxy, (1-6C)alkoxycarbonyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl,

and wherein any of the R^1 substituents defined hereinbefore which comprises a CH_2 group which is attached to 2 carbon atoms or a CH_3 group which is attached to a carbon or nitrogen atom may optionally bear on each said CH_2 or CH_3 group one or more substituents selected from halogeno, hydroxy, trifluoromethyl, (1-6C)alkyl, (3-6C)cycloalkyl, (1-6C)alkoxy, di-[(1-6C)alkyl]amino, (1-6C)alkoxy-(1-6C)alkyl, (1-6C)alkoxycarbonyl, heteroaryl-(1-6C)alkyl, heterocyclyl and heterocyclyloxy.

R^1 is fluoro, chloro, bromo, iodo, hydroxy, methoxy, ethoxy, propoxy, acetyl, methylthio, ethylthio, methylsulphonyl, ethylsulphonyl, 2-aminoethoxy, 2-amino-1-methylethoxy, 3-aminopropoxy, 2-amino-2-methylpropoxy, 2-methylaminoethoxy, 2-methylamino-1-methylethoxy, 3-ethylaminopropoxy, 2-dimethylaminoethoxy, 2-diethylaminoethoxy, 2-dimethylaminopropoxy, 2-dimethylamino- 2-methylethoxy, 3-dimethylaminopropoxy, dimethylaminomethyl, diethylaminomethyl, 1-dimethylaminoethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl., carbamoylmethyl, 1-carbamoylethyl, 2-carbamoylethyl, 3-carbamoylpropyl, heteroarylmethyl, heteroarylethyl, heterocyclyl, heterocyclyloxy, heterocyclylmethoxy and 2-heterocyclylethoxy,

and wherein any heteroaryl or heterocyclyl group in a R^1 substituent may optionally bear 1 or 2 substituents selected from hydroxy, is fluoro, chloro, bromo, iodo, methyl, ethyl, propyl, isopropyl, cyclobutylmethyl, cyclopropylmethyl, cyclobutylmethoxy, cyclopropylmethoxy, acetyl, methoxy, ethoxy, propoxy, methoxycarbonylmethyl, ethoxycarbonylmethyl, tert-butoxycarbonylmethyl, 1-methoxycarbonylethyl, 1-ethoxycarbonylethyl, 2-methoxycarbonylethyl, 2-ethoxycarbonylethyl, 3-methoxycarbonylpropyl, 3-ethoxycarbonylpropyl, N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl, N,N-dimethylcarbamoyl, N-ethyl-N-methylcarbamoyl, N,N-diethylcarbamoyl, fluoromethyl, chloromethyl, bromomethyl, difluoromethyl, dichloromethyl, dibromomethyl, 2-fluoroethyl, 2-chloroethyl, 2-bromoethyl, hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl, 3-hydroxypropyl, methoxymethyl, ethoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 2-ethoxyethyl and 3-methoxypropyl, cyanomethyl, 2-cyanoethyl, 1-cyanoethyl, 3-cyanopropyl,

and wherein any of the R^1 substituents defined hereinbefore which comprises a CH_2 group which is attached to 2 carbon atoms or a CH_3 group which is attached to a carbon or nitrogen atom may optionally bear on each said CH_2 or CH_3 group one or more substituents selected from fluoro, chloro, bromo, iodo, hydroxy, trifluoromethyl, methyl, ethyl, propyl, isopropyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, methoxy, ethoxy, propoxy, isopropoxy, tert-butoxy, dimethylamino, diethylamino, N-ethyl-N-methylamino, methoxymethyl, ethoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 2-ethoxyethyl, 3-methoxypropyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl,tert-butoxycarbonyl, heteroarylmethyl, heteroarylethyl, heterocyclyl and heterocyclyloxy.

R^1 is fluoro, chloro, bromo, iodo, hydroxy, methoxy, ethoxy, propoxy, acetyl, methylthio, ethylthio, methylsulphonyl, ethylsulphonyl, 2-aminoethoxy, 2-amino-1-methylethoxy, 3-aminopropoxy, 2-amino-2-methylpropoxy, 2-methylaminoethoxy, 2-methylamino-1-methylethoxy, 3-ethylaminopropoxy, 2-dimethylaminoethoxy, 2-diethylaminoethoxy, 2-dimethylaminopropoxy, 2-dimethylamino- 2-methylethoxy, 3-dimethylaminopropoxy, dimethylaminomethyl, diethylaminomethyl, 1-dimethylaminoethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl., carbamoylmethyl, 1-carbamoylethyl, 2-carbamoylethyl, 3-carbamoylpropyl, piperidinylmethyl, piperidinylethyl, homopiperidinyl, piperazinyl, homopiperazinyl, morpholinyl, dihydropyridinyl, tetrahydropyridinyl,

dihydropyrimidinyl or tetrahydropyrimidinyl, piperidinyloxy, pyrrolodinyloxy, morpholinylethoxy, pyrrolidinylethoxy, piperidinylethoxy, azetidinylethoxy, , and wherein any heteroaryl or heterocyclyl group in a R^1 substituent may optionally bear 1 or 2 substituents selected from hydroxy, is fluoro, chloro, bromo, iodo, methyl, ethyl, propyl, isopropyl, cyclobutylmethyl, cyclopropylmethyl, cyclobutylmethoxy, cyclopropylmethoxy, acetyl, methoxy, ethoxy, propoxy, methoxycarbonylmethyl, ethoxycarbonylmethyl, tert-butoxycarbonylmethyl, 1-methoxycarbonylethyl, 1-ethoxycarbonylethyl, 2-methoxycarbonylethyl, 2-ethoxycarbonylethyl, 3-methoxycarbonylpropyl, 3-ethoxycarbonylpropyl, N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl, N,N-dimethylcarbamoyl, N-ethyl-N-methylcarbamoyl, N,N-diethylcarbamoyl, fluoromethyl, chloromethyl, bromomethyl, difluoromethyl, dichloromethyl, dibromomethyl, 2-fluoroethyl, 2-chloroethyl, 2-bromoethyl, hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl, 3-hydroxypropyl, methoxymethyl, ethoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 2-ethoxyethyl and 3-methoxypropyl, cyanomethyl, 2-cyanoethyl, 1-cyanoethyl, 3-cyanopropyl,

and wherein any of the R^1 substituents defined hereinbefore which comprises a CH_2 group which is attached to 2 carbon atoms or a CH_3 group which is attached to a carbon or nitrogen atom may optionally bear on each said CH_2 or CH_3 group one or more substituents selected from fluoro, chloro, bromo, iodo, hydroxy, trifluoromethyl, methyl, ethyl, propyl, isopropyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, methoxy, ethoxy, propoxy, isopropoxy, tert-butoxy, dimethylamino, diethylamino, N-ethyl-N-methylamino, methoxymethyl, ethoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 2-ethoxyethyl, 3-methoxypropyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl,tert-butoxycarbonyl, piperidinylmethyl, piperidinylethyl, homopiperidinyl, piperazinyl, homopiperazinyl, morpholinyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyrimidinyl, tetrahydropyrimidinyl, piperidinyloxy andpyrrolodinyloxy.

R^1 is amino-(2-6C)alkoxy, (1-6C)alkylamino-(2-6C)alkoxy, di-[(1-6C)alkyl]amino-(2-6C)alkoxy, amino-(2-6C)alkylamino, (1-6C)alkylamino-(2-6C)alkylamino, di-[(1-6C)alkyl]amino-(2-6C)alkylamino, aryl, aryl-(1-6C)alkyl, aryl-(1-6C)alkoxy, aryloxy, arylamino, heteroaryl, heteroaryl-(1-6C)alkyl, heteroaryloxy, heteroaryl-(1-6C)alkoxy, heteroarylamino, heterocyclyl, heterocyclyl-(1-6C)alkyl, heterocyclyloxy, heterocyclyl-(1-6C)alkoxy or heterocyclylamino,

and wherein any aryl, heteroaryl or heterocyclyl group in a R^1 substituent may optionally bear 1 or 2 substituents selected from hydroxy, halogeno, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl-(1-6C)alkyl, (3-6C)cycloalkyl-(1-6C)alkoxy, (1-6C)alkoxy, carboxy, (1-6C)alkoxycarbonyl, (1-6C)alkoxycarbonyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, carboxy-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl,

and wherein any of the R^1 substituents defined hereinbefore which comprises a CH_2 group which is attached to 2 carbon atoms or a CH_3 group which is attached to a carbon atom may optionally bear on each said CH_2 or CH_3 group one or more substituents selected from hydroxy, amino, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino,

and wherein any heterocyclyl group in a R^1 substituent may optionally bear 1 or 2 oxo or thioxo substituents.

R^1 is aryl, aryl-(1-6C)alkyl, aryl-(1-6C)alkoxy, aryloxy, arylamino, heteroaryl, heteroaryl-(1-6C)alkyl, heteroaryloxy, heteroaryl-(1-6C)alkoxy, heteroarylamino, heterocyclyl, heterocyclyl-(1-6C)alkyl, heterocyclyloxy, heterocyclyl-(1-6C)alkoxy or heterocyclylamino,

and wherein any aryl, heteroaryl or heterocyclyl group in a R^1 substituent may optionally bear 1 or 2 substituents selected from hydroxy, halogeno, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl-(1-6C)alkyl, (3-6C)cycloalkyl-(1-6C)alkoxy, (1-6C)alkoxy, carboxy, (1-6C)alkoxycarbonyl, (1-6C)alkoxycarbonyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, carboxy-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl,

and wherein any of the R^1 substituents defined hereinbefore which comprises a CH_2 group which is attached to 2 carbon atoms or a CH_3 group which is attached to a carbon atom may optionally bear on each said CH_2 or CH_3 group one or more substituents selected from hydroxy, amino, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino,

and wherein any heterocyclyl group in a R^1 substituent may optionally bear 1 or 2 oxo or thioxo substituents.

R^1 is amino-(2-6C)alkoxy, (1-6C)alkylamino-(2-6C)alkoxy, di-[(1-6C)alkyl]amino-(2-6C)alkoxy, amino-(2-6C)alkylamino, (1-6C)alkylamino-(2-6C)alkylamino or di-[(1-6C)alkyl]amino-(2-6C)alkylamino,

and wherein any of the R^1 substituents defined hereinbefore which comprises a CH_2 group which is attached to 2 carbon atoms or a CH_3 group which is attached to a carbon atom may optionally bear on each said CH_2 or CH_3 group one or more substituents selected from hydroxy, amino, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino.

R^1 is heterocyclyl, heterocyclyl-(1-6C)alkyl, heterocycloxy, heterocyclyl-(1-6C)alkoxy or heterocyclylamino,

and wherein any heterocyclyl group in a R^1 substituent may optionally bear 1 or 2 substituents selected from hydroxy, halogeno, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl-(1-6C)alkyl, (3-6C)cycloalkyl-(1-6C)alkoxy, (1-6C)alkoxy, carboxy, (1-6C)alkoxycarbonyl, (1-6C)alkoxycarbonyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, carboxy-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl,

and wherein any of the R^1 substituents defined hereinbefore which comprises a CH_2 group which is attached to 2 carbon atoms or a CH_3 group which is attached to a carbon atom may optionally bear on each said CH_2 or CH_3 group one or more substituents selected from hydroxy, amino, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino.

R^1 is heterocyclyl, heterocyclyloxy or heterocyclyl-(1-6C)alkoxy,

and wherein any heterocyclyl group in a R^1 substituent may optionally bear 1 or 2 substituents selected from hydroxy, halogeno, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl-(1-6C)alkyl, (3-6C)cycloalkyl-(1-6C)alkoxy, (1-6C)alkoxy, carboxy, (1-6C)alkoxycarbonyl, (1-6C)alkoxycarbonyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl,

(1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, carboxy-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl, and wherein any of the R^1 substituents defined hereinbefore which comprises a CH_2 group which is attached to 2 carbon atoms or a CH_3 group which is attached to a carbon atom may optionally bear on each said CH_2 or CH_3 group one or more substituents selected from hydroxy, amino, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino.

R^1 is heterocyclyl or heterocyclyloxy,

and wherein any heterocyclyl group in a R^1 substituent may optionally bear 1 or 2 substituents selected from hydroxy, halogeno, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl-(1-6C)alkyl, (3-6C)cycloalkyl-(1-6C)alkoxy, (1-6C)alkoxy, carboxy, (1-6C)alkoxycarbonyl, (1-6C)alkoxycarbonyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, carboxy-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl, and wherein any of the R^1 substituents defined hereinbefore which comprises a CH_2 group which is attached to 2 carbon atoms or a CH_3 group which is attached to a carbon atom may optionally bear on each said CH_2 or CH_3 group one or more substituents selected from hydroxy, amino, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino.

R^1 is a non-aromatic saturated or partially saturated 3- to 10-membered monocyclic or bicyclic ring or a 5- to 7-membered monocyclic ring each with up to five heteroatoms selected from oxygen, nitrogen and sulphur,

and wherein any group in a R^1 substituent may optionally bear 1 or 2 substituents selected from hydroxy, halogeno, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl-(1-6C)alkyl, (3-6C)cycloalkyl-(1-6C)alkoxy, (1-6C)alkoxy, carboxy, (1-6C)alkoxycarbonyl, (1-6C)alkoxycarbonyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, carboxy-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl,

and wherein any of the R^1 substituents defined hereinbefore which comprises a CH_2 group which is attached to 2 carbon atoms or a CH_3 group which is attached to a carbon atom may optionally bear on each said CH_2 or CH_3 group one or more substituents selected from hydroxy, amino, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino.

R^1 is heterocyclyl or heterocyclyloxy,

and wherein any heterocyclyl group in a R^1 substituent may optionally bear 1 or 2 substituents selected from (1-6C)alkyl, (3-6C)cycloalkyl-(1-6C)alkyl, (1-6C)alkoxycarbonyl, (1-6C)alkoxycarbonyl-(1-6C)alkyl and hydroxy-(1-6C)alkyl.

R^1 is morpholinyl, thiomorpholinyl, piperidinyl, piperidinyloxy, homopiperidinyl, piperazinyl or homopiperazinyl,

and wherein any group in a R^1 substituent may optionally bear 1 or 2 substituents selected from hydroxy, halogeno, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl-(1-6C)alkyl, (3-6C)cycloalkyl-(1-6C)alkoxy, (1-6C)alkoxy, carboxy, (1-6C)alkoxycarbonyl, (1-6C)alkoxycarbonyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, carboxy-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl,

and wherein any of the R^1 substituents defined hereinbefore which comprises a CH_2 group which is attached to 2 carbon atoms or a CH_3 group which is attached to a carbon atom may optionally bear on each said CH_2 or CH_3 group one or more substituents selected from hydroxy, amino, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino.

R^1 is morpholinyl, thiomorpholinyl, piperidinyl, piperidinyloxy, homopiperidinyl, piperazinyl or homopiperazinyl,

and wherein any heterocyclyl group in a R^1 substituent may optionally bear 1 or 2 substituents selected from (1-6C)alkyl, (3-6C)cycloalkyl-(1-6C)alkyl, (1-6C)alkoxycarbonyl, (1-6C)alkoxycarbonyl-(1-6C)alkyl and hydroxy-(1-6C)alkyl.

R^1 is piperidinyl, piperidinyloxy, homopiperidinyl, piperazinyl or homopiperazinyl,

and wherein any group in a R^1 substituent may optionally bear 1 or 2 substituents selected from methyl, ethyl, propyl, isopropyl, cyclopropylmethyl, tert-butoxycarbonyl, tert-butoxycarbonylmethyl and 2-hydroxyethyl.

R^1 is 4-methylpiperazin-1yl.

R^2 is halogeno, trifluoromethyl or (1-6C)alkyl.

R^2 is trifluoromethyl or (1-6C)alkyl.

R^2 is trifluoromethyl or methyl.

R^2 is methyl.

R^3 is hydrogen, halogeno or (1-6C)alkyl;

R^3 is hydrogen or halogeno.

R^3 is hydrogen or chloro.

R^3 is chloro.

R^3 is hydrogen.

R^4 is (3-6C)cycloalkyl, and R^4 may be optionally substituted by one or more substituents selected from halogeno, hydroxy, amino, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino.

R^4 is (3-5C)cycloalkyl, and R^4 may be optionally substituted by one or more substituents selected from halogeno, hydroxy, amino, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino.

R^4 is cyclopropyl, cyclobutyl, or cyclopentyl, and R^4 may be optionally substituted by one or more substituents selected from halogeno, hydroxy, amino, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino.

R^4 is cyclopropyl or cyclobutyl, and R^4 may be optionally substituted by one or more substituents selected from halogeno, hydroxy, amino, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino.

R^4 is cyclopropyl and may be optionally substituted by one or more substituents selected from halogeno, hydroxy, amino, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino.

R^4 is cyclopropyl and may be optionally substituted by one or more substituents selected from halogeno, hydroxy, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl and (1-6C)alkoxy.

R^4 is cyclopropyl and may be optionally substituted by one or more substituents selected from fluoro, chloro, hydroxy, methyl, ethyl, and methoxy.

R^4 is cyclopropyl and may be optionally substituted by methyl and methoxy.

R^4 is cyclopropyl and may be optionally substituted by methyl.

R^4 is cyclopropyl, cyclobutyl or cyclopentyl.

R^4 is cyclopropyl or cyclobutyl.

R^4 is cyclopropyl.

Particular novel compounds of the invention include, for example, amide derivatives of the Formula I, or pharmaceutically-acceptable salts thereof, wherein:-

(a) m is 1;

R^1 is heterocyclyl, heterocyclyl-(1-6C)alkyl, heterocyclyloxy, heterocyclyl-(1-6C)alkoxy or heterocyclylamino,

and wherein any heterocyclyl group in a R^1 substituent may optionally bear 1 or 2 substituents selected from hydroxy, halogeno, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl-(1-6C)alkyl, (3-6C)cycloalkyl-(1-6C)alkoxy, (1-6C)alkoxy, carboxy, (1-6C)alkoxycarbonyl, (1-6C)alkoxycarbonyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, carboxy-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl,

and wherein any of the R^1 substituents defined hereinbefore which comprises a CH_2 group which is attached to 2 carbon atoms or a CH_3 group which is attached to a carbon atom may optionally bear on each said CH_2 or CH_3 group one or more substituents selected from hydroxy, amino, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino;

R^2 is trifluoromethyl or methyl;

R^3 is hydrogen or chloro; and

R^4 is (3-6C)cycloalkyl, and R^4 may be optionally substituted by one or more substituents selected from halogeno, hydroxy, amino, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl,(1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino.

(b) m is 1;

R^1 is heterocyclyl or heterocyclyloxy,

and wherein any heterocyclyl group in a R^1 substituent may optionally bear 1 or 2 substituents selected from hydroxy, halogeno, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl-(1-6C)alkyl, (3-6C)cycloalkyl-(1-6C)alkoxy, (1-6C)alkoxy, carboxy, (1-6C)alkoxycarbonyl, (1-6C)alkoxycarbonyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, carboxy-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl,

and wherein any of the R^1 substituents defined hereinbefore which comprises a CH_2 group which is attached to 2 carbon atoms or a CH_3 group which is attached to a carbon atom may optionally bear on each said CH_2 or CH_3 group one or more substituents selected from hydroxy, amino, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino;

R^2 is methyl;

R^3 is hydrogen; and

R^4 is cyclopropyl and may be optionally substituted by one or more substituents selected from halogeno, hydroxy, amino, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl,(1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino.

(c) m is 1;

R^1 is heterocyclyl or heterocyclyloxy,

and wherein any heterocyclyl group in a R^1 substituent may optionally bear 1 or 2 substituents selected from (1-6C)alkyl, (3-6C)cycloalkyl-(1-6C)alkyl, (1-6C)alkoxycarbonyl, (1-6C)alkoxycarbonyl-(1-6C)alkyl and hydroxy-(1-6C)alkyl;

R^2 is methyl;

R^3 is hydrogen; and

R^4 is cyclopropyl and may be optionally substituted by one or more substituents selected from halogeno, hydroxy, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl and (1-6C)alkoxy.

(d) m is 1;

R^1 is morpholinyl, thiomorpholinyl, piperidinyl, piperidinyloxy, homopiperidinyl, piperazinyl or homopiperazinyl,

and wherein any heterocyclyl group in a R^1 substituent may optionally bear 1 or 2 substituents selected from (1-6C)alkyl, (3-6C)cycloalkyl-(1-6C)alkyl, (1-6C)alkoxycarbonyl, (1-6C)alkoxycarbonyl-(1-6C)alkyl and hydroxy-(1-6C)alkyl.

R^2 is methyl;

R^3 is hydrogen; and

R^4 is cyclopropyl or cyclobutyl.

(e) m is 1;

R^1 is piperidinyl, piperidinyloxy, homopiperidinyl, piperazinyl or homopiperazinyl, and wherein any group in a R^1 substituent may optionally bear 1 or 2 substituents selected from methyl, ethyl, propyl, isopropyl, cyclopropylmethyl, tert-butoxycarbonyl, tert-butoxycarbonylmethyl and 2-hydroxyethyl;

R^2 is methyl;

R^3 is hydrogen; and

R^4 is cyclopropyl or cyclobutyl.

(f) m is 1;

R^1 is halogeno, hydroxy, cyano, trifluoromethyl, trifluoromethoxy, (1-6C)alkyl, (1-6C)alkoxy, (2-6C)alkenyl, (2-6C)alkynyl, (2-6C)alkanoyl, (1-6C)alkylthio, (1-6C)alkylsulphonyl, hydroxy-(2-6C)alkoxy, amino-(2-6C)alkoxy, cyano-(2-6C)alkoxy, (1-6C)alkylamino-(2-6C)alkoxy, di-[(1-6C)alkyl]amino-(2-6C)alkoxy, (1-6C)alkoxy-(2-6C)alkoxy, di[(1-6C)alkyl]amino-(1-6C)alkyl, carbamoyl-(1-6C)alkyl, heteroaryl-(1-6C)alkyl, heteroaryl-(1-6C)alkoxy, heterocyclyl, heterocyclyl-(1-6C)alkyl, heterocyclyloxy and heterocyclyl-(1-6C)alkoxy,

and wherein any heteroaryl or heterocyclyl group in a R^1 substituent may optionally bear 1 or 2 substituents selected from hydroxy, halogeno, (1-6C)alkyl, (3-6C)cycloalkyl-(1-6C)alkyl, (3-6C)cycloalkyl-(1-6C)alkoxy, (1-6C)alkoxy, (1-6C)alkoxycarbonyl, (1-6C)alkoxycarbonyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl,

and wherein any of the R^1 substituents defined hereinbefore which comprises a CH_2 group which is attached to 2 carbon atoms or a CH_3 group which is attached to a carbon or nitrogen atom may optionally bear on each said CH_2 or CH_3 group one or more substituents selected from halogeno, hydroxy, trifluoromethyl, oxo (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl,

(3-6C)cycloalkyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, halogeno-(1-6C)alkyl, (1-6C)alkoxycarbonyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl and heterocyclyloxy, and wherein any heterocyclyl group in a R^1 substituent may optionally bear 1 or 2 oxo or thioxo substituents;

R^2 is trifluoromethyl or methyl;

R^3 is hydrogen;

R^4 is cyclopropyl or cyclobutyl and may be optionally substituted by one or more substituents selected from fluoro, chloro, hydroxy, methyl, ethyl, and methoxy.

(g) m is 1;

R^1 is halogeno, hydroxy, (1-6C)alkoxy, (2-6C)alkenyl, (2-6C)alkynyl, (2-6C)alkanoyl, (1-6C)alkylthio, (1-6C)alkylsulphonyl, amino-(2-6C)alkoxy, (1-6C)alkylamino-(2-6C)alkoxy, di-[(1-6C)alkyl]amino-(2-6C)alkoxy, di[(1-6C)alkyl]amino-(1-6C)alkyl, carbamoyl-(1-6C)alkyl, heteroaryl-(1-6C)alkyl, heterocyclyl, heterocyclyloxy and heterocyclyl-(1-6C)alkoxy,

and wherein any heteroaryl or heterocyclyl group in a R^1 substituent may optionally bear 1 or 2 substituents selected from hydroxy, halogeno, (1-6C)alkyl, (3-6C)cycloalkyl-(1-6C)alkyl, (3-6C)cycloalkyl-(1-6C)alkoxy, (1-6C)alkoxy, (1-6C)alkoxycarbonyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl,

and wherein any of the R^1 substituents defined hereinbefore which comprises a CH_2 group which is attached to 2 carbon atoms or a CH_3 group which is attached to a carbon or nitrogen atom may optionally bear on each said CH_2 or CH_3 group one or more substituents selected from halogeno, hydroxy, trifluoromethyl, (1-6C)alkyl, (3-6C)cycloalkyl, (1-6C)alkoxy, di-[(1-6C)alkyl]amino, (1-6C)alkoxy-(1-6C)alkyl, (1-6C)alkoxycarbonyl, heteroaryl-(1-6C)alkyl, heterocyclyl and heterocyclyloxy;

R^2 is methyl;

R^3 is hydrogen;

R^4 is cyclopropyl or cyclobutyl and may be optionally substituted by one or more substituents selected from fluoro, chloro, hydroxy, methyl, ethyl, and methoxy.

(h) m is 1;

R^1 is fluoro, chloro, bromo, iodo, hydroxy, methoxy, ethoxy, propoxy, acetyl, methylthio, ethylthio, methylsulphonyl, ethylsulphonyl, 2-aminoethoxy, 2-amino-1-methylethoxy, 3-aminopropoxy, 2-amino-2-methylpropoxy, 2-methylaminoethoxy, 2-methylamino-1-methylethoxy, 3-ethylaminopropoxy, 2-dimethylaminoethoxy, 2-diethylaminoethoxy, 2-dimethylaminopropoxy, 2-dimethylamino- 2-methylethoxy, 3-dimethylaminopropoxy, dimethylaminomethyl, diethylaminomethyl, 1-dimethylaminoethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl., carbamoylmethyl, 1-carbamoylethyl, 2-carbamoylethyl, 3-carbamoylpropyl, heteroarylmethyl, heteroarylethyl, heterocyclyl, heterocyclyloxy, heterocyclylmethoxy and 2-heterocyclylethoxy,

and wherein any heteroaryl or heterocyclyl group in a R^1 substituent may optionally bear 1 or 2 substituents selected from hydroxy, is fluoro, chloro, bromo, iodo, methyl, ethyl, propyl, isopropyl, cyclobutylmethyl, cyclopropylmethyl, cyclobutylmethoxy, cyclopropylmethoxy, acetyl, methoxy, ethoxy, propoxy, methoxycarbonylmethyl, ethoxycarbonylmethyl, tert-butoxycarbonylmethyl, 1-methoxycarbonylethyl, 1-ethoxycarbonylethyl, 2-methoxycarbonylethyl, 2-ethoxycarbonylethyl, 3-methoxycarbonylpropyl, 3-ethoxycarbonylpropyl, N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl, N,N-dimethylcarbamoyl, N-ethyl-N-methylcarbamoyl, N,N-diethylcarbamoyl, fluoromethyl, chloromethyl, bromomethyl, difluoromethyl, dichloromethyl, dibromomethyl, 2-fluoroethyl, 2-chloroethyl, 2-bromoethyl, hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl, 3-hydroxypropyl, methoxymethyl, ethoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 2-ethoxyethyl and 3-methoxypropyl, cyanomethyl, 2-cyanoethyl, 1-cyanoethyl, 3-cyanopropyl,

and wherein any of the R^1 substituents defined hereinbefore which comprises a CH_2 group which is attached to 2 carbon atoms or a CH_3 group which is attached to a carbon or nitrogen atom may optionally bear on each said CH_2 or CH_3 group one or more substituents selected from fluoro, chloro, bromo, iodo, hydroxy, trifluoromethyl, methyl, ethyl, propyl, isopropyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, methoxy, ethoxy, propoxy, isopropoxy, tert-butoxy, dimethylamino, diethylamino, N-ethyl-N-methylamino, methoxymethyl, ethoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 2-ethoxyethyl, 3-methoxypropyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl,tert-butoxycarbonyl, heteroarylmethyl, heteroarylethyl, heterocyclyl and heterocyclyloxy

R^2 is methyl;

R^3 is hydrogen;

R^4 is cyclopropyl or cyclobutyl and may be optionally substituted by methyl.

(i) m is 1;

R^1 is fluoro, chloro, bromo, iodo, hydroxy, methoxy, ethoxy, propoxy, acetyl, methylthio, ethylthio, methylsulphonyl, ethylsulphonyl, 2-aminoethoxy, 2-amino-1-methylethoxy, 3-aminopropoxy, 2-amino-2-methylpropoxy, 2-methylaminoethoxy, 2-methylamino-1-methylethoxy, 3-ethylaminopropoxy, 2-dimethylaminoethoxy, 2-diethylaminoethoxy, 2-dimethylaminopropoxy, 2-dimethylamino- 2-methylethoxy, 3-dimethylaminopropoxy, dimethylaminomethyl, diethylaminomethyl, 1-dimethylaminoethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl., carbamoylmethyl, 1-carbamoylethyl, 2-carbamoylethyl, 3-carbamoylpropyl, piperidinylmethyl, piperidinylethyl, homopiperidinyl, piperazinyl, homopiperazinyl, morpholinyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyrimidinyl or tetrahydropyrimidinyl, piperidinyloxy, pyrrolodinyloxy, morpholinylethoxy, pyrrolidinylethoxy, piperidinylethoxy, azetidinylethoxy, ,

and wherein any heteroaryl or heterocyclyl group in a R^1 substituent may optionally bear 1 or 2 substituents selected from hydroxy, fluoro, chloro, bromo, iodo, methyl, ethyl, propyl, isopropyl, cyclobutylmethyl, cyclopropylmethyl, cyclobutylmethoxy, cyclopropylmethoxy, acetyl, methoxy, ethoxy, propoxy, methoxycarbonylmethyl, ethoxycarbonylmethyl, tert-butoxycarbonylmethyl, 1-methoxycarbonylethyl, 1-ethoxycarbonylethyl, 2-methoxycarbonylethyl, 2-ethoxycarbonylethyl, 3-methoxycarbonylpropyl, 3-ethoxycarbonylpropyl, N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl, N,N-dimethylcarbamoyl, N-ethyl-N-methylcarbamoyl, N,N-diethylcarbamoyl, fluoromethyl, chloromethyl, bromomethyl, difluoromethyl, dichloromethyl, dibromomethyl, 2-fluoroethyl, 2-chloroethyl, 2-bromoethyl, hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl, 3-hydroxypropyl, methoxymethyl, ethoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 2-ethoxyethyl and 3-methoxypropyl, cyanomethyl, 2-cyanoethyl, 1-cyanoethyl, 3-cyanopropyl,

and wherein any of the R^1 substituents defined hereinbefore which comprises a CH_2 group which is attached to 2 carbon atoms or a CH_3 group which is attached to a carbon or nitrogen atom may optionally bear on each said CH_2 or CH_3 group one or more substituents selected from fluoro, chloro, bromo, iodo, hydroxy, trifluoromethyl, methyl, ethyl, propyl, isopropyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, methoxy, ethoxy, propoxy, isopropoxy, tert-

butoxy, dimethylamino, diethylamino, N-ethyl-N-methylamino, methoxymethyl, ethoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 2-ethoxyethyl, 3-methoxypropyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl,tert-butoxycarbonyl, piperidinylmethyl, piperidinylethyl, homopiperidinyl, piperazinyl, homopiperazinyl, morpholinyl, dihydropyridinyl, tetrahydropyridinyl, dihydropyrimidinyl, tetrahydropyrimidinyl, piperidinyloxy andpyrrolodinyloxy

R^2 is methyl;

R^3 is hydrogen;

R^4 is cyclopropyl or cyclobutyl and may be optionally substituted by methyl.

A particular preferred compound of the invention is, for example :-

N-cyclopropyl-4-methyl-3-[6-(4-methylpiperazin-1-yl)-4-oxoquinazolin-3(4H)-yl]benzamide,
N-cyclobutyl-4-methyl-3-[6-(4-methylpiperazin-1-yl)-4-oxoquinazolin-3(4H)-yl]benzamide,
N-cyclopropyl-4-methyl-3-[4-oxo-6-(piperidin-4-yloxy)quinazolin-3(4H)-yl]benzamide,
N-cyclopropyl-3-[6-{[1-(cyclopropylmethyl)piperidin-4-yl]oxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide,
N-cyclopropyl-3-[6-(1,4-diazepan-1-yl)-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide,
N-cyclopropyl-4-methyl-3-(4-oxo-6-piperazin-1-ylquinazolin-3(4H)-yl)benzamide,
N-cyclopropyl-4-methyl-3-[6-(4-methyl-1,4-diazepan-1-yl)-4-oxoquinazoline-3(4H)-yl]benzamide,
N-cyclopropyl-4-methyl-3-[6-(4-ethylpiperazin-1-yl)-4-oxoquinazoline-3(4H)-yl]benzamide,
N-cyclopropyl-4-methyl-3-[6-(4-isopropylpiperazin-1-yl)-4-oxoquinazoline-3(4H)-yl]benzamide,
N-cyclopropyl-4-methyl-3-[6-[(3S)-3-methylpiperazin-1-yl]-4-oxoquinazoline-3(4H)-yl]benzamide,
N-cyclopropyl-4-methyl-3-[6-[(3R)-3-methylpiperazin-1-yl]-4-oxoquinazoline-3(4H)-yl]benzamide,
N-cyclopropyl-4-methyl-3-[6-[4-(2-hydroxyethyl) piperazin-1-yl]-4-oxoquinazoline-3(4H)-yl]benzamide,
N-cyclopropyl-4-methyl-3-[4-oxo-6-(4-propylpiperazin-1-yl)quinazolin-3(4H)-yl]benzamide,
N-cyclopropyl-4-methyl-3-[4-oxo-6-(4-propyl-1,4-diazepan-1-yl)quinazolin-3(4H)-yl]benzamide,
N-cyclopropyl-4-trifluoromethyl-3-[6-(4-methylpiperazin-1-yl)-4-oxoquinazolin-3(4H)-

yl]benzamide,

N-cyclopropyl-4-methyl-3-[6-(4-[tert-butylacetyl]piperazin-1-yl)-4-oxoquinazoline-3(4H)-yl]benzamide,

N-cyclopropyl-4-methyl-3-[6-[(3S)-3,4-dimethylpiperazin-1-yl)]-4-oxoquinazoline-3(4H)-yl]benzamide,

N-cyclopropyl-4-methyl-3-[6-[(3R)-3,4-dimethylpiperazin-1-yl]-4-oxoquinazoline-3(4H)-yl]benzamide,

N-cyclopentyl-4-methyl-3-[6-(4-methylpiperazin-1-yl)-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-3-[6-[(3-hydroxy-2,2-dimethylpropyl)amino]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[2-methyl-6-(4-methyl-1,4-diazepan-1-yl)-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-3-[6-[4-(cyclopropylmethyl)-1,4-diazepan-1-yl]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-(4-ethyl-1,4-diazepan-1-yl)-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-[4-(2-methoxyethyl)-1,4-diazepan-1-yl]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

3-[6-[4-(2-amino-2-oxoethyl)-1,4-diazepan-1-yl]-4-oxoquinazolin-3(4H)-yl]-N-cyclopropyl-4-methylbenzamide;

[4-(3-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4-oxo-3,4-dihydroquinazolin-6-yl)piperazin-1-yl]acetic acid;

N-cyclopropyl-3-[6-[4-(cyclopropylmethyl)piperazin-1-yl]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-[4-(2-ethoxyethyl)piperazin-1-yl]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-2-methyl-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-(7-fluoro-4-oxoquinazolin-3(4H)-yl)-4-methylbenzamide;

N-cyclopropyl-3-[6-(2,3-dihydroxy-2-methylpropoxy)-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-(6-isobutoxy-4-oxoquinazolin-3(4H)-yl)-4-methylbenzamide;

N-cyclopropyl-3-[6-(2-hydroxy-2-methyl-3-pyrrolidin-1-ylpropoxy)-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-(6-morpholin-4-yl-4-oxoquinazolin-3(4H)-yl)benzamide;

N-cyclopropyl-4-methyl-3-(4-oxo-6-thiomorpholin-4-ylquinazolin-3(4H)-yl)benzamide;

N-cyclopropyl-3-[6-(4-hydroxypiperidin-1-yl)-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-(3-hydroxyazetidin-1-yl)-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[6-(4-methyl-4-oxidopiperazin-1-yl)-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-[6-[4-(methylsulfonyl)piperazin-1-yl]-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-3-[6-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[6-(4-methylpiperidin-1-yl)-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-(4-oxo-6-piperidin-1-ylquinazolin-3(4H)-yl)benzamide;

4-methyl-N-(1-methylcyclopropyl)-3-[6-(4-methylpiperazin-1-yl)-4-oxoquinazolin-3(4H)-yl]benzamide;

3-[6-[4-(cyanomethyl)piperazin-1-yl]-4-oxoquinazolin-3(4H)-yl]-N-cyclopropyl-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[4-oxo-6-(4-prop-2-yn-1-ylpiperazin-1-yl)quinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-(4-oxoquinazolin-3(4H)-yl)benzamide;

3-[6-(4-acetylpiperazin-1-yl)-4-oxoquinazolin-3(4H)-yl]-N-cyclopropyl-4-methylbenzamide;

3-[6-(4-cyclobutylpiperazin-1-yl)-4-oxoquinazolin-3(4H)-yl]-N-cyclopropyl-4-methylbenzamide;

N-cyclopropyl-3-(6-iodo-4-oxoquinazolin-3(4H)-yl)-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[6-[(1-methylpiperidin-4-yl)oxy]-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-3-(6-methoxy-4-oxoquinazolin-3(4H)-yl)-4-methylbenzamide;

3-[6-(4-isopropylpiperazin-1-yl)-4-oxoquinazolin-3(4H)-yl]-4-methyl-N-(1-methylcyclopropyl)benzamide;

N-cyclobutyl-3-[6-(4-isopropylpiperazin-1-yl)-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-[(1-ethylpiperidin-4-yl)oxy]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[7-(4-methylpiperazin-1-yl)-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-3-[6-[(1-isopropylpiperidin-4-yl)oxy]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[4-oxo-6-[4-(1,3-thiazol-4-ylmethyl)piperazin-1-yl]quinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-[6-{4-[(5-methylisoxazol-3-yl)methyl]piperazin-1-yl}-4-oxoquinazolin-3(4H)-yl]benzamide;

tert-butyl 3-[(3-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4-oxo-3,4-dihydroquinazolin-6-yl)oxy]pyrrolidine-1-carboxylate;

N-cyclopropyl-4-methyl-3-[4-oxo-6-(pyrrolidin-3-yloxy)quinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-[4-oxo-6-(pyridin-2-ylmethoxy)quinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-3-[6-[4-(2-fluoroethyl)piperazin-1-yl]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-[4-(2,2-difluoroethyl)piperazin-1-yl]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[4-oxo-6-{4-[2-(tetrahydro-2H-pyran-2-yloxy)ethyl]piperazin-1-yl}quinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-[6-[(1-methylpyrrolidin-3-yl)oxy]-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-3-[6-[(1-ethylpyrrolidin-3-yl)oxy]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-{[1-(cyclopropylmethyl)pyrrolidin-3-yl]oxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-{[1-(2-fluoroethyl)piperidin-4-yl]oxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-{[1-(2-methoxyethyl)piperidin-4-yl]oxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-[2-(dimethylamino)ethoxy]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-[(1-cyclopropylpiperidin-4-yl)oxy]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-[(3R)-4-ethyl-3-methylpiperazin-1-yl]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[7-fluoro-6-(4-methylpiperazin-1-yl)-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-[(3R)-4-isopropyl-3-methylpiperazin-1-yl]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-[(3R)-4-(cyclopropylmethyl)-3-methylpiperazin-1-yl]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[4-oxo-6-(2-pyrrolidin-1-ylethoxy)quinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-[6-(2-morpholin-4-ylethoxy)-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-[4-oxo-6-(2-piperidin-1-ylethoxy)quinazolin-3(4H)-yl]benzamide;

3-[6-(2-azetidin-1-ylethoxy)-4-oxoquinazolin-3(4H)-yl]-N-cyclopropyl-4-methylbenzamide;

tert-butyl 5-(3-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4-oxo-3,4-dihydroquinazolin-6-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate;

N-cyclopropyl-3-[6-[3-(dimethylamino)propoxy]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-[(1-isopropylpyrrolidin-3-yl)oxy]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[6-(5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl)-4-oxoquinazolin-3(4*H*)-yl]benzamide;

N-cyclopropyl-3-(6-hydroxy-4-oxoquinazolin-3(4H)-yl)-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[4-oxo-6-(1,2,3,6-tetrahydropyridin-4-yl)quinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-3-[6-[2-(4-isopropylpiperazin-1-yl)ethoxy]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-[2-(4,4-difluoropiperidin-1-yl)ethoxy]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-{2-[(3R)-3-fluoropyrrolidin-1-yl]ethoxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[4-oxo-6-[(3S)-pyrrolidin-3-yloxy]quinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-[6-[2-(1,4-oxazepan-4-yl)ethoxy]-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-[6-{2-[methyl(pyridin-2-ylmethyl)amino]ethoxy}-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-[4-oxo-6-[4-(2,2,2-trifluoro-1-methylethyl)piperazin-1-yl]quinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-3-[6-{2-[(2-methoxyethyl)(methyl)amino]ethoxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-(4-oxopyrido[3,4-d]pyrimidin-3(4H)-yl)benzamide;

N-cyclopropyl-4-methyl-3-[6-{[(3S)-1-methylpyrrolidin-3-yl]oxy}-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-3-[6-{[(3S)-1-ethylpyrrolidin-3-yl]oxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-{[(3S)-1-(cyclopropylmethyl)pyrrolidin-3-yl]oxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-{[(3S)-1-isopropylpyrrolidin-3-yl]oxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-(4-oxopyrido[2,3-d]pyrimidin-3(4H)-yl)benzamide;

N-cyclopropyl-4-methyl-3-[4-oxo-6-[(3R)-pyrrolidin-3-yloxy]quinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-[4-oxo-6-(3-piperidin-1-ylpropoxy)quinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-[4-oxo-6-[2-(1H-pyrrol-1-yl)ethoxy]quinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-[4-oxo-6-(3-pyrrolidin-1-ylpropoxy)quinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-3-[6-[2-(dimethylamino)-2-methylpropoxy]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[4-oxo-6-[3-(1H-pyrrol-1-yl)propoxy]quinazolin-3(4H)-yl]benzamide;

3-[6-(2-aminoethoxy)-4-oxoquinazolin-3(4H)-yl]-N-cyclopropyl-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[6-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-3-[6-{[(3R)-1-ethylpyrrolidin-3-yl]oxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-{[(3R)-1-(cyclopropylmethyl)pyrrolidin-3-yl]oxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-{[(3R)-1-isopropylpyrrolidin-3-yl]oxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-[2-(dimethylamino)-2-oxoethoxy]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[6-{2-[(methylsulfonyl)amino]ethoxy}-4-oxoquinazolin-3(4H)-yl]benzamide;

3-[6-[2-(acetylamino)ethoxy]-4-oxoquinazolin-3(4H)-yl]-N-cyclopropyl-4-methylbenzamide;

N-cyclopropyl-3-(7-methoxy-4-oxoquinazolin-3(4H)-yl)-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[6-[3-(4-methylpiperazin-1-yl)propoxy]-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-[6-[(1-methylpiperidin-3-yl)methoxy]-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-3-[6-[2-(1H-imidazol-1-yl)ethoxy]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[4-oxo-6-[2-(2-oxoimidazolidin-1-yl)ethoxy]quinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-[6-[(1-methylpiperidin-2-yl)methoxy]-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-[6-[(1-methyl-1H-imidazol-2-yl)methoxy]-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-3-[6-{[2-(dimethylamino)ethyl]thio}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[4-oxo-6-(2-thiomorpholin-4-ylethoxy)quinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-3-[6-[2-(4-hydroxypiperidin-1-yl)ethoxy]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

3-[6-{2-[(cyclobutylmethyl)(methyl)amino]ethoxy}-4-oxoquinazolin-3(4H)-yl]-N-cyclopropyl-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[6-(2-{methyl[2-(methylsulfonyl)ethyl]amino}ethoxy)-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-[6-(2-{methyl[(1-methyl-1H-pyrazol-4-yl)methyl]amino}ethoxy)-4-oxoquinazolin-3(4H)-yl]benzamide;

methyl (2E)-3-(3-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4-oxo-3,4-dihydroquinazolin-6-yl)acrylate;

N-cyclopropyl-3-[6-[3-(dimethylamino)prop-1-yn-1-yl]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-[3-(dimethylamino)propyl]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[6-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-[6-(1-methylpiperidin-4-yl)-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-3-[7-[3-(dimethylamino)propoxy]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[7-(2-morpholin-4-ylethoxy)-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-3-[6-{[1-(2-hydroxy-2-methylpropyl)piperidin-4-yl]oxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-({1-[(2S)-2-hydroxypropyl]piperidin-4-yl}oxy)-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-({1-[(2R)-2-hydroxypropyl]piperidin-4-yl}oxy)-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[4-oxo-6-[(2S)-pyrrolidin-2-ylmethoxy]quinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-[6-{[(2S)-1-methylpyrrolidin-2-yl]methoxy}-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-3-[6-{[1-(2-hydroxyethyl)piperidin-4-yl]oxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-{2-[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]ethoxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-{2-[(2S)-2-(methoxymethyl)pyrrolidin-1-yl]ethoxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-{2-[isopropyl(methyl)amino]ethoxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-{2-[isopropyl(2-methoxyethyl)amino]ethoxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

3-[6-[2-(tert-butylamino)ethoxy]-4-oxoquinazolin-3(4H)-yl]-N-cyclopropyl-4-methylbenzamide;

N-cyclopropyl-3-[6-[3-(dimethylamino)-2-methylpropoxy]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[6-[(4-methylmorpholin-2-yl)methoxy]-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-[8-(4-methylpiperazin-1-yl)-4-oxoquinazolin-3(4H)-yl]benzamide;

3-[6-[2-(dimethylamino)ethoxy]-4-oxoquinazolin-3(4H)-yl]-4-methyl-N-(1-methylcyclopropyl)benzamide;

4-methyl-N-(1-methylcyclopropyl)-3-[4-oxo-6-(2-piperidin-1-ylethoxy)quinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-3-(8-methoxy-4-oxoquinazolin-3(4H)-yl)-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[4-oxo-6-[(2R)-pyrrolidin-2-ylmethoxy]quinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-[6-{[(2R)-1-methylpyrrolidin-2-yl]methoxy}-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-3-[6-{[(2S)-1-glycoloylpyrrolidin-2-yl]methoxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[4-oxo-6-(3-thiomorpholin-4-ylpropoxy)quinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-3-[6-{3-[(3R)-3-hydroxypyrrolidin-1-yl]propoxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-[3-(4-hydroxypiperidin-1-yl)propoxy]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-{3-[(2-methoxyethyl)(methyl)amino]propoxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

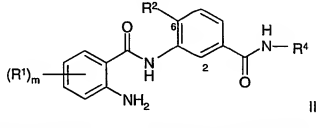
N-cyclopropyl-3-[6-{3-[(3-furylmethyl)(methyl)amino]propoxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide; and

3-[6-{3-[(cyclobutylmethyl)(methyl)amino]propoxy}-4-oxoquinazolin-3(4H)-yl]-N-cyclopropyl-4-methylbenzamide;

or a pharmaceutically-acceptable salt thereof.

Compounds of the Formula I, or a pharmaceutically-acceptable salts thereof, may be prepared by any process known to be applicable to the preparation of chemically-related compounds. Suitable processes are illustrated by, for example, those in WO 00/55153. Such processes, when used to prepare a novel compound of the Formula I are provided as a further feature of the invention and are illustrated by the following representative process variants in which, unless otherwise stated, R^1, R^2, R^3 and R^4 have any of the meanings defined hereinbefore. Necessary starting materials may be obtained by standard procedures of organic chemistry. The preparation of such starting materials is described in conjunction with the following representative process variants and within the accompanying Examples. Alternatively necessary starting materials are obtainable by analogous procedures to those illustrated which are within the ordinary skill of an organic chemist.

(a) A compound of the Formula I, or a pharmaceutically-acceptable salt thereof, may be prepared by reacting an N-phenyl-2-aminobenzamide of the Formula II



II

with a carboxylic acid of the Formula III, or a reactive derivative thereof,

III

wherein variable groups are as defined hereinbefore and wherein any functional group is protected if necessary, and:

(i) removing any protecting groups; and

(ii) optionally forming a pharmaceutically-acceptable salt.

A suitable reactive derivative of a carboxylic acid of the Formula III is, for example, an acyl halide, for example an acyl chloride formed by the reaction of the acid and an inorganic acid chloride, for example thionyl chloride; a mixed anhydride, for example an anhydride formed by the reaction of the acid and a chloroformate such as isobutyl chloroformate; an active ester, for example an ester formed by the reaction of the acid with a phenol such as pentafluorophenol, with an ester such as pentafluorophenyl trifluoroacetate or with an alcohol such as N-hydroxybenzotriazole; an acyl azide, for example an azide formed by the reaction of the acid and an azide such as diphenylphosphoryl azide; an acyl cyanide, for example a cyanide formed by the reaction of an acid and a cyanide such as diethylphosphoryl cyanide; or the product of the reaction of the acid and a carbodiimide such as dicyclohexylcarbodiimide. A preferred reactive derivative of a carboxylic acid of the Formula III is, for example, an ester of the corresponding ortho acid of the carboxylic acid of the Formula III, for example a trialkyl ester such as a trimethyl or triethyl ester. For a carboxylic acid of the Formula III wherein R^3 is hydrogen, a suitable ortho acid ester is triethyl orthoformate and for a carboxylic acid of the Formula III wherein R^3 is methyl, a suitable ortho acid ester is triethyl orthoacetate.

The reaction may conveniently be carried out in the presence of a suitable base such as, for example, an alkali or alkaline earth metal carbonate, alkoxide, hydroxide or hydride, for example sodium carbonate, potassium carbonate, sodium ethoxide, potassium butoxide, sodium hydroxide, potassium hydroxide, sodium hydride or potassium hydride, or an organometallic base such as an alkyl-lithium, for example n-butyl-lithium, or a dialkylamino-lithium, for example lithium di-isopropylamide, or, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine or diazabicyclo[5.4.0]undec-7-ene.

The reaction may also conveniently be carried out in the presence of a suitable acid

such as, for example, an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric, acetic, trifluoroacetic, citric or maleic acid.

The reaction is also preferably carried out in a suitable inert solvent or diluent, for example methanol, ethanol, tetrahydrofuran, methylene chloride, 1,2-dimethoxyethane, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one, dimethylsulphoxide or acetone, and at a temperature in the range, for example, 0 to 150°C, conveniently at or near 75°C.

Protecting groups may in general be chosen from any of the groups described in the literature or known to the skilled chemist as appropriate for the protection of the group in question and may be introduced by conventional methods. Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Specific examples of protecting groups are given below for the sake of convenience, in which "lower", as in, for example, lower alkyl, signifies that the group to which it is applied preferably has 1-4 carbon atoms. It will be understood that these examples are not exhaustive. Where specific examples of methods for the removal of protecting groups are given below these are similarly not exhaustive. The use of protecting groups and methods of deprotection not specifically mentioned is of course within the scope of the invention.

A carboxy protecting group may be the residue of an ester-forming aliphatic or arylaliphatic alcohol or of an ester-forming silanol (the said alcohol or silanol preferably containing 1-20 carbon atoms). Examples of carboxy protecting groups include straight or branched chain (1-12C)alkyl groups (for example isopropyl, tert-butyl); lower alkoxy lower alkyl groups (for example methoxymethyl, ethoxymethyl, isobutoxymethyl); lower aliphatic acyloxy lower alkyl groups, (for example acetoxymethyl, propionyloxymethyl, butyryloxymethyl, pivaloyloxymethyl); lower alkoxycarbonyloxy lower alkyl groups (for example 1-methoxycarbonyloxyethyl, 1-ethoxycarbonyloxyethyl); aryl lower alkyl groups (for example benzyl, p-methoxybenzyl, o-nitrobenzyl, p-nitrobenzyl, benzhydryl and phthalidyl); tri(lower alkyl)silyl groups (for example trimethylsilyl and tert-butyldimethylsilyl); tri(lower alkyl)silyl lower alkyl groups (for example trimethylsilylethyl); and (2-6C)alkenyl groups (for example allyl and vinylethyl). Methods particularly appropriate for the removal of carboxyl

protecting groups include for example acid-, base-, metal- or enzymically-catalysed hydrolysis.

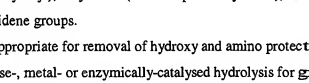
Examples of hydroxy protecting groups include lower alkyl groups (for example tert-butyl), lower alkenyl groups (for example allyl); lower alkanoyl groups (for example acetyl); lower alkoxycarbonyl groups (for example tert-butoxycarbonyl); lower alkenyloxycarbonyl groups (for example allyloxycarbonyl); aryl lower alkoxycarbonyl groups (for example benzoyloxycarbonyl, p-methoxybenzyloxycarbonyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl); tri lower alkylsilyl (for example trimethylsilyl, tert-butyldimethylsilyl) and aryl lower alkyl (for example benzyl) groups.

Examples of amino protecting groups include formyl, aralkyl groups (for example benzyl and substituted benzyl, p-methoxybenzyl, nitrobenzyl and 2,4-dimethoxybenzyl, and triphenylmethyl); di-p-anisylmethyl and furylmethyl groups; lower alkoxycarbonyl (for example tert-butoxycarbonyl); lower alkenyloxycarbonyl (for example allyloxycarbonyl); aryl lower alkoxycarbonyl groups (for example benzyloxycarbonyl, p-methoxybenzyloxycarbonyl, o-nitrobenzyloxycarbonyl, p-nitrobenzyloxycarbonyl; trialkylsilyl (for example trimethylsilyl and tert-butyldimethylsilyl); alkylidene (for example methylidene); benzylidene and substituted benzylidene groups.

Methods appropriate for removal of hydroxy and amino protecting groups include, for example, acid-, base-, metal- or enzymically-catalysed hydrolysis for groups such as p-nitrobenzyloxycarbonyl, hydrogenation for groups such as benzyl and photolytically for groups such as o-nitrobenzyloxycarbonyl.

The reader is referred to Advanced Organic Chemistry, 4th Edition, by Jerry March, published by John Wiley & Sons 1992, for general guidance on reaction conditions and reagents. The reader is referred to Protective Groups in Organic Synthesis, 2nd Edition, by Green *et al.*, published by John Wiley & Sons for general guidance on protecting groups.

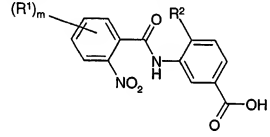
The N-phenyl-2-aminobenzamide of the Formula II may be prepared by reduction of the corresponding nitro compound of the Formula IV



IV

Typical reaction conditions include the use of ammonium formate or hydrogen gas in the presence of a catalyst, for example a metallic catalyst such as palladium-on-carbon. Alternatively a dissolving metal reduction may be carried out, for example using iron in the presence of an acid, for example an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric or acetic acid. The reaction is conveniently carried out in the presence of an organic solvent (preferably a polar protic solvent) and preferably with heating, for example to about 60°C. Any functional groups are protected and deprotected as necessary.

The nitrobenzene of the Formula IV may be prepared by the reaction of the acid of the Formula V, or a reactive derivative thereof as defined hereinbefore



V

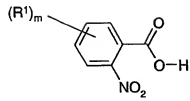
with a amine of the Formula VI,

VI

under standard amide bond forming conditions, wherein variable groups are as defined hereinbefore and wherein any functional group is protected if necessary.

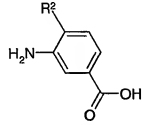
Typical conditions include activating the carboxy group of the compound of Formula V, for example by treatment with a halo reagent (for example oxalyl chloride) to form an acyl halide in an organic solvent at ambient temperature and then reacting the activated compound with the amine of Formula VI. Any functional groups are protected and deprotected as necessary. Conveniently a carbodiimide coupling reagent is used in the presence of an organic solvent (preferably an anhydrous polar aprotic organic solvent) at a non-extreme temperature, for example in the region -10 to 40°C, typically at ambient temperature of about 20°C.

An acid of the Formula V may be prepared by the reaction of a benzoic acid of Formula VII, or an activated derivative thereof as defined hereinbefore,



VII

with an aniline of Formula VIII



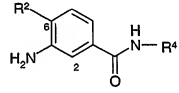
VIII

wherein variable groups are as defined hereinbefore and wherein the carboxy group is protected as necessary, and:

(i) removing any protecting groups;

under suitable amide bond forming conditions as defined hereinbefore.

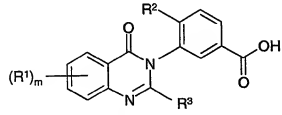
The nitrobenzene of Formula IV may also be prepared by the reaction of a benzoic acid of Formula VII, or an activated derivative thereof as defined hereinbefore, with an aniline of Formula IX



IX

under suitable amide bond forming conditions as defined hereinbefore;

(b) A compound of the Formula I or a pharmaceutically-acceptable salt thereof, may be prepared by reacting a carboxylic acid of the Formula X or a reactive derivative thereof as defined hereinbefore,



X

with a amine of the Formula VI,

VI

under standard amide bond forming conditions as defined hereinbefore, wherein variable groups are as defined hereinbefore and wherein any functional group is protected if necessary, and:

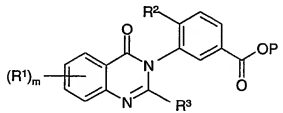
(i) removing any protecting groups; and

(ii) optionally forming a pharmaceutically-acceptable salt.

The reaction is preferably carried out in the presence of a suitable base as defined hereinbefore The reaction is preferably carried out in a suitable inert solvent or diluent, for example tetrahydrofuran, methylene chloride, 1,2-dimethoxyethane, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one, dimethylsulphoxide or acetone, and at a temperature in the range, for example, -78 to 150°C, conveniently at or near ambient temperature.

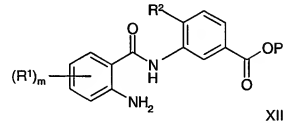
Typically a carbodiimide coupling reagent is used in the presence of an organic solvent (preferably an anhydrous polar aprotic organic solvent) at a non-extreme temperature, for example in the region -10 to 40°C, typically at ambient temperature of about 20°C. Other typical conditions include activating the carboxy group of the compound of Formula X, for example by treatment with a halo reagent (for example oxalyl or thionyl chloride) to form an acyl halide in an organic solvent at ambient temperature and then reacting the activated compound with the amine of Formula VI.

A carboxylic acid of the Formula X may be prepared by deprotection under standard conditions as defined hereinbefore of the corresponding protected carboxy compound of the Formula XI, wherein P is a carboxy protecting group (such as an ester), as defined hereinbefore. Typically this transformation is achieved using an aqueous solution of sodium hydroxide or anhydrous sodium methoxide in an alcoholic medium, such as methanol in the region of 40 – 65°C to give the carboxylate salt. The desired carboxylic acid X is recovered by addition of an aqeous acid, typically dilute hydrochloric acid.



XI

The protected carboxy compound of the Formula XI may be prepared by reacting an N-phenyl-2-aminobenzamide of the Formula XII



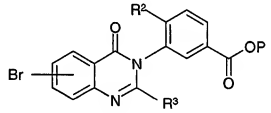
XII

with a carboxylic acid of the Formula III, or a reactive derivative thereof,

III

wherein variable groups are as defined hereinbefore and wherein any functional group is protected if necessary.

The protected carboxy compound of the Formula XI may also be prepared by reacting an aryl bromide of the formula XIII

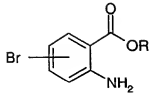


XIII

with an $(R^1)_m$-amine under standard amination forming conditions, wherein variable groups are as defined hereinbefore and wherein any functional group is protected if necessary.

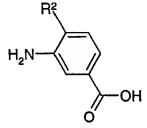
Typical conditions include the use of a suitable transition metal catalyst precursor, such as Palladium Acetate in the presence of a chelating bidentate phosphine ligand, such as BINAP with an inorganic base such as cesium carbonate. Conveniently, aromatic solvents such as toluene is used for this transformation at temperature, for example in the region 80 to 110°C, typically at temperature of about 100°C. The transformation may also be effected using the aryl iodides or aryl triflate versions of a compound of the formula XIII.

The Aryl Bromide compound of the Formula XIII may be prepared by reacting a commercially available substituted anthranilic acid derivative of the formula XIV wherein R is hydrogen or (1-6C)alkyl,



XIV

with an aniline of Formula VIII



VIII

and reacting the resultant compound with a carboxylic acid of the Formula IX, or a reactive derivative thereof,

IX

wherein variable groups are as defined hereinbefore and wherein any functional group is protected if necessary, and:

(i) removing any protecting groups; and

(ii) optionally forming a pharmaceutically-acceptable.

A suitable reactive derivative of a carboxylic acid of the Formula IX is, for example, an acyl halide, for example an acyl chloride formed by the reaction of the acid and an inorganic acid chloride, for example thionyl chloride; a mixed anhydride, for example an anhydride formed by the reaction of the acid and a chloroformate such as isobutyl chloroformate; an active ester, for example an ester formed by the reaction of the acid with a phenol such as pentafluorophenol, with an ester such as pentafluorophenyl trifluoroacetate or with an alcohol such as N-hydroxybenzotriazole; an acyl azide, for example an azide formed by the reaction of the acid and an azide such as diphenylphosphoryl azide; an acyl cyanide, for example a cyanide formed by the reaction of an acid and a cyanide such as diethylphosphoryl cyanide; or the product of the reaction of the acid and a carbodiimide such as

dicyclohexylcarbodiimide. A preferred reactive derivative of a carboxylic acid of the Formula IX is, for example, an ester of the corresponding ortho acid of the carboxylic acid of the Formula IX, for example a trialkyl ester such as a trimethyl or triethyl ester. For a carboxylic acid of the Formula IX wherein R^3 is hydrogen, a suitable ortho acid ester is triethyl orthoformate and for a carboxylic acid of the Formula IX wherein R^3 is methyl, a suitable ortho acid ester is triethyl orthoacetate.

The reaction requires an acid catalyst such as sulphuric, *p*-toluenesulfonic, formic, benzoic, acetic and trifluoroacetic.

The reaction is also preferably carried out in a suitable inert solvent, for example, ethanol, n-Butanol, 2-Methyl-Butan-2-ol (*tert*-Amyl alcohol), cyclohexanol, n-butyl acetate, propionitrile, 4-Methyl-2-Pentanone (MIBK), N-methylpyrrolidinone, acetic acid, anisole and toluene at a temperature in the range, for example, 78 to 120°C, conveniently at or near 100°C.

(c) A compound of the Formula I wherein a substituent on R^1 or R^4 is (1-6C)alkoxy or substituted (1-6C)alkoxy, (1-6C)alkylamino or di-[(1-6C)alkyl]amino may be prepared by the alkylation, conveniently in the presence of a suitable base as defined hereinbefore, of a compound of the Formula I wherein wherein a substituent on R^1 or R^4 is hydroxy or amino as appropriate.

The reaction is preferably carried out in the presence of a suitable inert solvent or diluent, for example a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride, an ether such as tetrahydrofuran or 1,4-dioxan, an aromatic solvent such as toluene, or a dipolar aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one or dimethylsulphoxide. The reaction is conveniently carried out at a temperature in the range, for example, 10 to 150°C, preferably in the range 20 to 80°C.

A suitable alkylating agent is, for example, any agent known in the art for the alkylation of hydroxy to alkoxy or substituted alkoxy, or for the alkylation of amino to alkylamino or substituted alkylamino, for example an alkyl or substituted alkyl halide, for example a (1-6C)alkyl chloride, bromide or iodide or a substituted (1-6C)alkyl chloride, bromide or iodide, in the presence of a suitable base as defined hereinbefore, in a suitable inert solvent or diluent as defined hereinbefore and at a temperature in the range, for example, 10 to 140°C, conveniently at or near ambient temperature.

(d) A compound of the Formula I wherein a substituent a substituent on R^1 or R^4 is amino, (1-6C)alkylamino or di-[(1-6C)alkyl]amino may be prepared by the reaction, conveniently in the presence of a suitable base as defined hereinbefore, of a compound of the Formula I wherein a substituent on R^1 or R^4 is a suitable leaving group with an appropriate amine.

A suitable leaving group is, for example, a halogeno group such as fluoro, chloro or bromo, a (1-6C)alkanesulphonyloxy group such as methanesulphonyloxy or an arylsulphonyloxy group such as 4-toluenesulphonyloxy.

The reaction is conveniently carried out in the presence of a suitable inert diluent or carrier as defined hereinbefore and at a temperature in the range, for example, 20 to 200°C, conveniently in the range 75 to 150°C.

The following biological assays and Examples serve to illustrate the present invention.

Biological Assays

The following assays can be used to measure the p38 kinase-inhibitory, the TNF-inhibitory and anti-arthritic effects of compounds of the Formula I:

In vitro enzyme assay

The ability test compounds to inhibit the enzyme p38 kinase was assessed. Activity of the test compound against each of the p38α and p38β isoforms of the enzyme was determined.

Human recombinant MKK6 (GenBank Accesion Number G1209672) was isolated from Image clone 45578 (Genomics, 1996, 33, 151) and utilised to produce protein in the form of a GST fusion protein in a pGEX vector using analogous procedures to those disclosed by J. Han et al., Journal of Biological Chemistry, 1996, 271, 2886-2891. p38α (GenBank Accession Number G529039) and p38β (GenBank Accession Number G1469305) were isolated by PCR amplification of human lymphoblastoid cDNA (GenBank Accession Number GM1416) and human foetal brain cDNA [synthesised from mRNA (Clontech, catalogue no. 6525-1) using a Gibco superscript cDNA synthesis kit] respectively using oligonucleotides designed for the 5′ and 3′ ends of the human p38α and p38β genes using analogous procedures to those described by J.Han et al., Biochimica et Biophysica Acta, 1995, 1265, 224-227 and Y. Jiang et al., Journal of Biological Chemistry, 1996, 271, 17920-17926.

Both p38 protein isoforms were expressed in E.coli in PET vectors. Human recombinant p38α and p38β isoforms were produced as 5′ c-myc, 6His tagged proteins. Both MKK6 and the p38 proteins were purified using standard protocols: the GST MKK6 was

purified using a glutathione sepharose column and the p38 proteins were purified using nickel chelate columns.

The p38 enzymes were activated prior to use by incubation with MKK6 for 3 hours at 30°C. The unactivated E.coli-expressed MKK6 retained sufficient activity to fully activate both isoforms of p38. For p38α, the activation incubate comprised p38α (50µl of 10mg/ml), MKK6 (5µl of 12mg/ml), 'Kinase buffer' [550µl; pH 7.4 buffer comprising Tris HCl (50mM), EGTA (0.1mM), sodium orthovanadate (0.1mM) and β-mercaptoethanol (0.1%)], Mg [75µl of 100mM $Mg(OCOCH_3)_2$] and ATP (75µl of 1mM). The activation incubate for p38β was similar to the above except containing p38β enzyme (82µl at 3.05mg/ml) and 518µl "Kinase buffer". p38α and p38β activation incubates were either used fresh or aliquoted and stored at -80°C.

The test compound was solubilised in DMSO (10mM) and 1:3 serial dilutions in DMSO carried out in polypropylene plates (Costar 3365). Compound dilutions were then diluted 1:10 in "Kinase buffer" and 10µl transferred to a microtiter assay plate (Costar 3596). Control wells contained 10µl (1:10 dilution in kinase buffer) DMSO. 'Kinase Assay Mix' [30µl; comprising Myelin Basic Protein (Sigma M-1891; 0.5ml of a 6.66mg/ml solution in "Kinase buffer"), activated p38α enzyme (3.8µl) and 'Kinase Buffer' (2.55ml)] was then added. Control wells on each plate either contained the above "Kinase Assay Mix" (n=6 replicates) or contained "Kinase Assay Mix" in which the activated p38 enzyme was replaced by Kinase buffer (n=6 replicates). 'Labelled ATP' was then added to all wells [10µl; comprising 50µM ATP, 5µCi ^{33}P ATP (Amersham International cat. no. AH9968) and 50mM $Mg(OCOCH_3)_2$]. For p38β, 23µl activated p38β enzyme and "Kinase buffer" (2.53 ml) were included in the "Kinase Assay Mix". The final concentration of test compound was 2.4µM–0.001µM (n=2 replicates). Microtiter plates were incubated at ambient temperature (with gentle agitation) for 60 minutes and the reaction stopped by addition of 20% trichloroacetic acid (TCA) (50µl). The precipitate protein was captured onto filter plates (PerkinElmer 6005174) using a Packard Filtermate harvester (2% TCA wash) which was then dried overnight and 25µl MICROSCINT O (Packard O6013611) added to each well. Plates were counted on a Top Count scintillation counter. Dose response curves were generated using an in house automated data analysis package and an Origin curve fitting package.

In vitro cell-based assays

(i) **PBMC**

The ability of a test compound to inhibit TNFα production was assessed by using human peripheral blood mononuclear cells which synthesise and secrete TNFα when stimulated with lipopolysaccharide (LPS).

Peripheral blood mononuclear cells (PBMC) were isolated from heparinised (10 units/ml heparin) human blood by density centrifugation (Lymphoprep™ ; Nycomed). Mononuclear cells were resuspended in "Culture Medium" [RPMI 1640 medium (Sigma R0883) containing 50 units/ml penicillin, 50μg/ml streptomycin and 2mM glutamine] supplemented with 1% heat-inactivated human AB serum (Sigma H-1513)]. Compounds were solubilised in DMSO at a concentration of 20mM, diluted 1:100 in "culture medium" and serial dilutions carried out in "Culture Medium" containing 1% DMSO. PBMCs ($2.2x10^5$ cells in 160μl culture medium) were incubated with 20μl of varying concentrations of test compound (duplicate cultures) or 20μl culture medium containing 1% DMSO (control wells) for 30 minutes at 37°C in a humidified (5%CO_2/95% air) incubator (Corning 3595 ; 96 well flat-bottom tissue culture plates). 20μl lipopolysaccharide [LPS E.Coli 0111:B4 (Sigma L-4130), final concentration 0.1μg/ml] solubilised in "Culture Medium" was added to appropriate wells. 20μl Culture Medium was added to "medium alone" control wells. Six "LPS alone" and six "medium alone" controls were included on each 96 well plate.

The test compound was tested for TNFα inhibitory activity over a final concentration dose range of 20μM–0.0001μM. Each test included a known TNFα inhibitor i.e. the p38 MAPK inhibitor, SB203580 (Lee, J.C., et al (1994) Nature 372 p739-746). Plates were incubated for 24 hours at 37°C (humidified incubator) after which 100μl of the supernatant was removed from each well and stored at -80°C (96 well round-bottom plates; Corning 3799). TNFα levels were determined in each sample using a human TNFα ELISA (using R&D Systems paired antibodies, MAB610 and BAF210.

$$\% \text{ inhibition} = \frac{(\text{LPS alone - medium alone}) - (\text{test concentration - medium alone})}{(\text{LPS alone - medium alone})} \times 100$$

(ii) **Human Whole Blood**

The ability of a test compound to inhibit TNFα production was also assessed in a human whole blood assay. Human whole blood secretes TNFα when stimulated with LPS.

Heparinised (10 units/ml) human blood was obtained from volunteers. 160µl whole blood was added to 96 well round-bottom plates (Corning 3799). Compounds were solubilised in DMSO at a concentration of 10mM, diluted 1:100 in "culture medium" [RPMI 1640 medium (Sigma) containing 50 units/ml penicillin, 50µg/ml streptomycin and 2mM glutamine] and subsequently serial dilutions were made in culture medium containing 1% DMSO. 20µl of each test concentration was added to appropriate wells (triplicate cultures)(final concentration dose range of 10µM–0.0001µM). 20µl of RPMI culture medium containing 1% DMSO was added to control wells.

Plates were incubated for 30 minutes at 37°C (humidified incubator), prior to addition of 20µl LPS (final concentration 10µg/ml). Culture medium was added to control wells. Six "LPS alone" and six "medium alone" controls were included on each plate. A known TNFα synthesis/secretion inhibitor was included in each test. Plates were incubated for 6 hours at 37°C (humidified incubator). Plates were centrifuged (2000 rpm for 10 minutes) and 80µl plasma removed and stored at -80°C (Corning 3799 plates). TNFα levels were measured by ELISA using paired antibodies from R&D Systems (catalogue nos. MAB610 and BAF210).

In vivo assessment

The ability of a test compound to inhibit TNFα synthesis in vivo was assessed in a rat lipopolysaccharide (LPS) -challenge model. Briefly, compound was dosed orally (100–0.3mg/kg in 20% DMSO (Sigma D-2650) / 60% PEG 400 (Fisher Scientific P/3676/08) / 20% sterile de-ionised water ; 5 animals per group) to female Wistar Alderley Park (AP) rats (80-100g) at appropriate timepoints prior to challenge with LPS. Control animals (10 per group) were dosed vehicle alone. LPS (LPS E.Coli 0111:B4 ; Sigma L-4130) was administered intravenously (30µg in 0.2 ml sterile physiological saline (Phoenix Pharma Ltd). A control group were challenged with 0.2 ml sterile physiological saline. Blood was obtained 60 minutes later from anaesthetised animals and serum isolated after 2 hours incubation at ambient temperature (Sarstedt serum separator 1ml microtubes, ref 41.1500.005) and centrifugation. Serum samples were stored at -80 °C prior to determination of TNFα content by ELISA (R&D Systems rat TNFα Quantikine kit, catalogue no. SRTA00). % inhibition

TNFα calculated as

100 - [(compound treated – saline control) / LPS control – saline control) x100]

Test as anti-arthritic agent

Compound was tested for activity in a rat streptococcal cell-wall-induced arthritis model (SCW) [for further information see Carlson,R.P. and Jacobsen, P.B. (1999) Comparison of adjuvant and streptococcal cell-wall-induced arthritis in the rat. In *In Vivo* Models of Inflammation, eds Morgan, D.W. and Marshall, L.A., Birkhauser Verlag, Basel, Switzerland].

Briefly, female Lewis rats (160-180g) were sensitised by intra-articular injection of 5μg streptococcal cell wall (Lee Labs, PG-PS 100P) in 20μl sterile physiological saline into the left ankle. Responsiveness was assessed 3 days later and animals randomised. Arthritis was induced 21 days after sensitisation (designated day 0) by intravenous injection of 100μg scw (in 500μl sterile physiological saline). Compound was dosed orally(50-1 mg/kg once daily) (4 ml/kg) either before (day–1) or after disease onset (day+1) (10 animals per test group ; vehicle 0.5% (w/v) HPMC and 0.1%(w/v) polysorbate 80). Control animals (n=10) received vehicle alone. "Non-induced" control animals which were dosed with vehicle were also included (5 animals per group). Animals were weighed on a daily basis from day–1 and ankle diameters measured with Vernier callipers on a daily basis from day–1. At termination on day 6, left hind limbs were removed and fixed in 10% formalin for histological assessment.

Although the pharmacological properties of the compounds of the Formula I vary with structural change as expected, in general a compound of the Formula a gives over 50% inhibition of p38α and/or p38β at concentrations less than 1μM. No physiologically unacceptable toxicity was observed at the effective dose for compounds tested of the present invention.

The following table shows IC_{50} figures for a representative selection of compounds according to the invention when tested in the above assays:

Example	p38α (μM)	Human Whole Blood (μM)
Comparator Compound A	0.277	3.71
Comparator Compound B	0.041	3.85
2	0.023	0.034
6	0.054	0.435
6(a)	0.081	0.351
7	0.008	0.034
16	0.066	0.084
24	0.019	0.017
25	0.033	0.078

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises compound of the Formula I, or a pharmaceutically-acceptable salt thereof, in association with a pharmaceutically-acceptable diluent or carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition for use in the treatment of diseases mediated by cytokines which comprises compound of the Formula I, or a pharmaceutically-acceptable salt thereof, in association with a pharmaceutically-acceptable diluent or carrier.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or

preservative agents.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 0.5 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition.

The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula I of the invention will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine.

In using a compound of the Formula I for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.5 mg to 75 mg per kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.5 mg to 30 mg per kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.5 mg to 25 mg per kg body weight will be used. Oral administration is however preferred, particularly in tablet form. Typically, unit dosage forms will contain about 1 mg to 500 mg of a compound of this invention.

According to a further aspect of the invention there is provided a compound of the Formula I, or a pharmaceutically-acceptable salt thereof, for use in a method of treatment of the human or animal body by therapy.

According to a further aspect of the invention there is provided the use of a compound of the Formula I, or a pharmaceutically-acceptable salt thereof, in the manufacture of a medicament.

According to a further aspect of the invention there is provided the use of a compound of the Formula I, or a pharmaceutically-acceptable salt thereof, in the manufacture of a medicament for use in the treatment of medical conditions mediated by cytokines.

In a further aspect the present invention provides a method of treating diseases or medical conditions mediated by cytokines which comprises administering to a warm-blooded animal an effective amount of a compound of the Formula I, or a pharmaceutically-acceptable

salt thereof.

In a further aspect the present invention provides a method of treating a disease or medical condition mediated by cytokines which comprises administering to a warm-blooded animal in need thereof a cytokine inhibiting amount of a compound of the Formula I, or a pharmaceutically-acceptable salt thereof.

In a further aspect the present invention provides a method of treating a disease or medical condition mediated by the production or effect of cytokines which comprises administering to a warm-blooded animal in need thereof a cytokine inhibiting amount of a compound of the Formula I, or a pharmaceutically-acceptable salt thereof.

In a further aspect on the invention there is provided a method for inhibiting the production or effect of a cytokine in a warm-blooded animal in need thereof a p38 kinase inhibiting amount of a compound of the Formula I, or a pharmaceutically-acceptable salt thereof

In a further aspect the present invention provides the use of a compound of the Formula I, or a pharmaceutically-acceptable salt thereof, in the manufacture of a medicament for use in the treatment of diseases or medical conditions mediated by TNF, IL-1, IL-6 or IL-8.

In a further aspect the present invention provides a method of treating diseases or medical conditions mediated by TNF, IL-1, IL-6 or IL-8 which comprises administering to a warm-blooded animal an effective amount of a compound of the Formula I, or a pharmaceutically-acceptable salt thereof.

In a further aspect the present invention provides the use of a compound of the Formula I, or a pharmaceutically-acceptable salt thereof in the manufacture of a medicament for use in the treatment of diseases or medical conditions mediated by TNF.

In a further aspect the present invention provides a method of treating diseases or medical conditions mediated by TNF which comprises administering to a warm-blooded animal an effective amount of a compound of the Formula I, or a pharmaceutically-acceptable salt thereof.

In a further aspect the present invention provides the use of a compound of the Formula I, or a pharmaceutically-acceptable salt thereof, in the manufacture of a medicament for use in inhibiting TNF, IL-1, IL-6 or IL-8.

In a further aspect the present invention provides a method of inhibiting TNF, IL-1, IL-6 or IL-8 which comprises administering to a warm-blooded animal an effective amount of a

compound of the Formula I, or a pharmaceutically-acceptable salt thereof.

In a further aspect the present invention provides the use of a compound of the Formula I, or a pharmaceutically-acceptable salt thereof, in the manufacture of a medicament for use in inhibiting TNF.

In a further aspect the present invention provides a method of inhibiting TNF which comprises administering to a warm-blooded animal an effective amount of a compound of the Formula I, or a pharmaceutically-acceptable salt thereof.

In a further aspect the present invention provides a compound of the Formula I, or a pharmaceutically-acceptable salt thereof, in the manufacture of a medicament for use in the treatment of diseases or medical conditions mediated by p38 kinase.

In a further aspect the present invention provides a method of treating diseases or medical conditions mediated by p38 kinase which comprises administering to a warm-blooded animal an effective amount of a compound of the Formula I, or a pharmaceutically- acceptable salt thereof.

In a further aspect the present invention provides the use of a compound of the Formula I, or a pharmaceutically-acceptable salt thereof, in the manufacture of a medicament for use in the production of a p38 kinase inhibitory effect.

In a further aspect the present invention provides a method of providing a p38 kinase inhibitory effect which comprises administering to a warm-blooded animal an effective amount of a compound of the Formula I, or a pharmaceutically-acceptable salt thereof.

In a further aspect the present invention provides the use of a compound of the Formula I, or a pharmaceutically-acceptable thereof, in the manufacture of a medicament for use in the treatment of rheumatoid arthritis, asthma, chronic obstructive pulmonary disease, inflammatory bowel disease, multiple sclerosis, AIDS, septic shock, congestive heart failure, ischaemic heart disease or psoriasis.

In a further aspect the present invention provides a method of treating rheumatoid arthritis, asthma, chronic obstructive pulmonary disease, inflammatory bowel disease, multiple sclerosis, AIDS, septic shock, congestive heart failure, ischaemic heart disease or psoriasis which comprises administering to a warm-blooded animal an effective amount of a compound of the Formula I, or a pharmaceutically-acceptable salt thereof.

A compound of the Formula I may be used in combination with other drugs and therapies used in the treatment of disease states which would benefit from the inhibition of

cytokines, in particular TNF and IL-1. For example, a compound of the Formula I could be used in combination with drugs and therapies used in the treatment of rheumatoid arthritis, asthma, chronic obstructive pulmonary disease, inflammatory bowel disease, multiple sclerosis, AIDS, septic shock, congestive heart failure, ischaemic heart disease, psoriasis and the other disease states mentioned earlier in this specification.

For example, by virtue of its ability to inhibit cytokines, a compound of the Formula I is of value in the treatment of certain inflammatory and non-inflammatory diseases which are currently treated with a cyclooxygenase-inhibitory non-steroidal anti-inflammatory drug (NSAID) such as indomethacin, ketorolac, acetylsalicyclic acid, ibuprofen, sulindac, tolmetin and piroxicam. Co-administration of a compound of the Formula I of the present invention with a NSAID can result in a reduction of the quantity of the latter agent needed to produce a therapeutic effect. Thereby the likelihood of adverse side-effects from the NSAID such as gastrointestinal effects are reduced. Thus according to a further feature of the invention there is provided a pharmaceutical composition which comprises a compound of the Formula I, or a pharmaceutically-acceptable salt thereof, in conjunction or admixture with a cyclooxygenase inhibitory non-steroidal anti-inflammatory agent, and a pharmaceutically-acceptable diluent or carrier.

A compound of the Formula I may also be used with anti-inflammatory agents such as an inhibitor of the enzyme 5-lipoxygenase.

A compound of the Formula I may also be used in the treatment of conditions such as rheumatoid arthritis in combination with antiarthritic agents such as gold, methotrexate, steroids and penicillinamine, and in conditions such as osteoarthritis in combination with steroids.

A compound of the Formula I may also be administered in degradative diseases, for example osteoarthritis, with chondroprotective, anti-degradative and/or reparative agents such as Diacerhein, hyaluronic acid formulations such as Hyalan, Rumalon, Arteparon and glucosamine salts such as Antril.

A compound of the Formula I may be used in the treatment of asthma in combination with antiasthmatic agents such as steroids, bronchodilators and leukotriene antagonists.

In particular, for the treatment of the inflammatory diseases rheumatoid arthritis, psoriasis, inflammatory bowel disease, chronic obstructive pulmonary disease, asthma and allergic rhinitis a compound of the present invention may be combined with agents such as

TNF-α inhibitors such as anti-TNF monoclonal antibodies (such as Remicade, CDP-870 and D.sub2.E.sub7.) and TNF receptor immunoglobulin molecules (such as Enbrel.reg.), non-selective COX-1 / COX-2 inhibitors (such as piroxicam, diclofenac, propionic acids such as naproxen, flubiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, apazone, pyrazolones such as phenylbutazone, salicylates such as aspirin), COX-2 inhibitors (such as meloxicam, celecoxib, rofecoxib, valdecoxib and etoricoxib) low dose methotrexate, lefunomide; ciclesonide; hydroxychloroquine, d-penicillamine, auranofin or parenteral or oral gold.

The present invention still further relates to the combination of a compound of the Formula I together with a leukotriene biosynthesis inhibitor, 5-lipoxygenase (5-LO) inhibitor or 5-lipoxygenase activating protein (FLAP) antagonist such as zileuton; ABT-761; fenleuton; tepoxalin; Abbott-79175; Abbott-85761; N-(5-substituted)-thiophene-2-alkylsulfonamides; 2,6-di-tert-butylphenol hydrazones; methoxytetrahydropyrans such as Zeneca ZD-2138; the compound SB-210661; pyridinyl-substituted 2-cyanonaphthalene compounds such as L-739,010; 2-cyanoquinoline compounds such as L-746,530; indole and quinoline compounds such as MK-591, MK-886, and BAY x 1005.

The present invention still further relates to the combination of a compound of the Formula I together with a receptor antagonist for leukotrienes LTB.sub4., LTC.sub4., LTD.sub4., and LTE.sub4. selected from the group consisting of the phenothiazin-3-ones such as L-651,392; amidino compounds such as CGS-25019c; benzoxalamines such as ontazolast; benzenecarboximidamides such as BIIL 284/260; and compounds such as zafirlukast, ablukast, montelukast, pranlukast, verlukast (MK-679), RG-12525, Ro-245913, iralukast (CGP 45715A), and BAY x 7195.

The present invention still further relates to the combination of a compound of the Formula I together with a PDE4 inhibitor including inhibitors of the isoform PDE4D.

The present invention still further relates to the combination of a compound of the Formula I together with a antihistaminic H.sub1. receptor antagonists such as cetirizine, loratadine, desloratadine, fexofenadine, astemizole, azelastine, and chlorpheniramine.

The present invention still further relates to the combination of a compound of the Formula I together with a gastroprotective H.sub2. receptor antagonist.

The present invention still further relates to the combination of a compound of the Formula I together with an α.sub1.- and α.sub2.-adrenoceptor agonist vasoconstrictor

sympathomimetic agent, such as propylhexedrine, phenylephrine, phenylpropanolamine, pseudoephedrine, naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, and ethylnorepinephrine hydrochloride.

The present invention still further relates to the combination of a compound of the Formula I together with anticholinergic agents such as ipratropium bromide; tiotropium bromide; oxitropium bromide; pirenzepine; and telenzepine.

The present invention still further relates to the combination of a compound of the Formula I together with a β.sub1.- to β.sub4.-adrenoceptor agonists such as metaproterenol, isoproterenol, isoprenaline, albuterol, salbutamol, formoterol, salmeterol, terbutaline, orciprenaline, bitolterol mesylate, and pirbuterol; or methylxanthanines including theophylline and aminophylline; sodium cromoglycate; or muscarinic receptor (M1, M2, and M3) antagonist.

The present invention still further relates to the combination of a compound of the Formula I together with an insulin-like growth factor type I (IGF-1) mimetic.

The present invention still further relates to the combination of a compound of the Formula I together with an inhaled glucocorticoid with reduced systemic side effects, such as prednisone, prednisolone, flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate, and mometasone furoate.

The present invention still further relates to the combination of a compound of the Formula I together with an inhibitor of matrix metalloproteases (MMPs), i.e., the stromelysins, the collagenases, and the gelatinases, as well as aggrecanase; especially collagenase-1 (MMP-1), collagenase-2 (MMP-8), collagenase-3 (MMP-13), stromelysin-1 (MMP-3), stromelysin-2 (MMP-10), and stromelysin-3 (MMP-11) and MMP-12.

The present invention still further relates to the combination of a compound of the Formula I together with other modulators of chemokine receptor function such as CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10 and CCR11 (for the C-C family); CXCR1, CXCR3, CXCR4 and CXCR5 (for the C-X-C family) and CX_3CR1 for the $C\text{-}X_3\text{-}C$ family.

The present invention still further relates to the combination of a compound of the Formula I together with antiviral agents such as Viracept, AZT, aciclovir and famciclovir, and antisepsis compounds such as Valant.

The present invention still further relates to the combination of a compound of the Formula I together with cardiovascular agents such as calcium channel blockers, lipid lowering agents such as statins, fibrates, beta-blockers, Ace inhibitors, Angiotensin-2 receptor antagonists and platelet aggregation inhibitors.

The present invention still further relates to the combination of a compound of the Formula I together with CNS agents such as antidepressants (such as sertraline), anti-Parkinsonian drugs (such as deprenyl, L-dopa, Requip, Mirapex, MAOB inhibitors such as selegine and rasagiline, comP inhibitors such as Tasmar, A-2 inhibitors, dopamine reuptake inhibitors, NMDA antagonists, Nicotine agonists, Dopamine agonists and inhibitors of neuronal nitric oxide synthase), and anti-Alzheimer's drugs such as donepezil, tacrine, COX-2 inhibitors, propentofylline or metryfonate.

The present invention still further relates to the combination of a compound of the Formula I together with (i) tryptase inhibitors; (ii) platelet activating factor (PAF) antagonists; (iii) interleukin converting enzyme (ICE) inhibitors; (iv) IMPDH inhibitors; (v) adhesion molecule inhibitors including VLA-4 antagonists; (vi) cathepsins; (vii) MAP kinase inhibitors; (viii) glucose-6 phosphate dehydrogenase inhibitors; (ix) kinin-B.sub1. - and B.sub2. -receptor antagonists; (x) anti-gout agents, e.g., colchicine; (xi) xanthine oxidase inhibitors, e.g., allopurinol; (xii) uricosuric agents, e.g., probenecid, sulfinpyrazone, and benzbromarone; (xiii) growth hormone secretagogues; (xiv) transforming growth factor (TGFβ); (xv) platelet-derived growth factor (PDGF); (xvi) fibroblast growth factor, e.g., basic fibroblast growth factor (bFGF); (xvii) granulocyte macrophage colony stimulating factor (GM-CSF); (xviii) capsaicin cream; (xix) Tachykinin NK.sub1. and NK.sub3. receptor antagonists selected from the group consisting of NKP-608C; SB-233412 (talnetant); and D-4418; (xx) elastase inhibitors selected from the group consisting of UT-77 and ZD-0892; (xxi) TNF? converting enzyme inhibitors (TACE); (xxii) induced nitric oxide synthase inhibitors (iNOS) or (xxiii) chemoattractant receptor-homologous molecule expressed on TH2 cells, (CRTH2 antagonists).

A compound of the Formula I may also be used in combination with osteoporosis agents such as roloxifene, droloxifene, lasofoxifene or fosomax and immunosuppressant agents such as FK-506, rapamycin, cyclosporine, azathioprine, and methotrexate.

A compound of the Formula I may also be used in combination with existing therapeutic agents for the treatment of osteoarthritis. Suitable agents to be used in

combination include standard non-steroidal anti-inflammatory agents (hereinafter NSAID's) such as piroxicam, diclofenac, propionic acids such as naproxen, flubiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, apazone, pyrazolones such as phenylbutazone, salicylates such as aspirin, COX-2 inhibitors such as celecoxib, valdecoxib, rofecoxib and etoricoxib, analgesics and intraarticular therapies such as corticosteroids and hyaluronic acids such as hyalgan and synvisc and P2X7 receptor antagonists.

A compound of the Formula I can also be used in combination with existing therapeutic agents for the treatment of cancer. Suitable agents to be used in combination include:

(i) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan and nitrosoureas); antimetabolites (for example antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea, gemcitabine and paclitaxel (Taxol®); antitumour antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin); antimitotic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene and iodoxyfene), oestrogen receptor down regulators (for example fulvestrant), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5α-reductase such as finasteride;

(iii) Agents which inhibit cancer cell invasion (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function);

(iv) inhibitors of growth factor function, for example such inhibitors include growth factor antibodies, growth factor receptor antibodies (for example the anti-erbb2 antibody trastuzumab [Herceptin™] and the anti-erbb1 antibody cetuximab [C225]) , farnesyl

transferase inhibitors, tyrosine kinase inhibitors and serine/threonine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, AZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), for example inhibitors of the platelet-derived growth factor family and for example inhibitors of the hepatocyte growth factor family;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, (for example the anti-vascular endothelial cell growth factor antibody bevacizumab [Avastin™], compounds such as those disclosed in International Patent Applications WO 97/22596, WO 97/30035, WO 97/32856 and WO 98/13354) and compounds that work by other mechanisms (for example linomide, inhibitors of integrin $\alpha v\beta 3$ function and angiostatin);

(vi) vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO00/40529, WO 00/41669, WO01/92224, WO02/04434 and WO02/08213;

(vii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;

(viii) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; and

(ix) immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

If formulated as a fixed dose such combination products employ a compound of the Formula I within the dosage range described herein and the other pharmaceutically-active

agent within its approved dosage range. Sequential use is contemplated when a combination formulation is inappropriate.

Although a compound of the Formula I is primarily of value as a therapeutic agent for use in warm-blooded animals (including man), it is also useful whenever it is required to inhibit the effects of cytokines. Thus, it is useful as pharmacological standard for use in the development of new biological tests and in the search for new pharmacological agents.

The invention will now be illustrated in the following non-limiting Example in which, unless otherwise stated:-

(i) operations were carried out at ambient temperature, *i.e.* in the range 17 to 25°C and under an atmosphere of an inert gas such as argon unless otherwise stated;

(ii) evaporations were carried out by rotary evaporation *in vacuo* and work-up procedures were carried out after removal of residual solids by filtration;

(iii) column chromatography (by the flash procedure) and medium pressure liquid chromatography (MPLC) were performed on Merck Kieselgel silica (Art. 9385) or Merck Lichroprep RP-18 (Art. 9303) reversed-phase silica obtained from E. Merck, Darmstadt, Germany or high pressure liquid chromatography (HPLC) was performed on C18 reverse phase silica, for example on a Dynamax C-18 60Å preparative reversed-phase column;

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) the structure of a compound of the Formula I of the invention was confirmed by nuclear magnetic resonance (NMR) and mass spectral techniques; fast-atom bombardment (FAB) mass spectral data were obtained using a Platform spectrometer and, where appropriate, either positive ion data or negative ion data were collected; NMR chemical shift values were measured on the delta scale [proton magnetic resonance spectra were determined using a Varian Gemini 2000 spectrometer operating at a field strength of 300MHz or a Bruker AM250 spectrometer operating at a field strength of 250MHz]; the following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad;

(vi) melting points are uncorrected and were determined using a Mettler SP62 automatic melting point apparatus or an oil-bath apparatus; and

(vii) the following abbreviations have been used:-

DMA *N*,*N*-dimethylacetamide

DMF *N*,*N*-dimethylformamide

DMSO	dimethylsulphoxide
THF	tetrahydrofuran
HATU	*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate

Example 1

***N*-cyclopropyl-4-methyl-3-[6-(4-methyl-1,4-diazepan-1-yl)-4-oxoquinazoline-3(4*H*)-yl]benzamide**

Triethylorthoformate (0.549 ml) was added to a stirred mixture of 2-amino-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-(4-methyl-1,4-diazepan-1-yl)benzamide (0.270 g) and glacial acetic acid (0.047 ml) in ethanol (5 ml). The mixture was heated to 80°C and stirred for 16 hours. The reaction mixture was evaporated, dissolved in methylene chloride and washed with a saturated $NaHCO_3$ solution. The organic phase was evaporated and the residue was purified by column chromatography on an ion exchange column (isolute SCX column from International Sorbent Technology Limited, Henoed, Mid-Glamorgan, UK) using initially methanol and then a 99:1 mixture of methanol and aqueous ammonia solution to give the title compound (0.102 g); NMR Spectrum: ($DMSOd_6$) 0.54 (m, 2H), 0.67 (m, 2H), 1.91 (m, 2H), 2.11 (s, 3H), 2.24 (s, 3H), 2.44 (m, 2H), 2.64 (t, 2H), 2.84 (m, 1H), 3.52 (t, 2H), 3.60 (t, 2H), 7.22 (d, 1H), 7.36 (m, 1H), 7.50 (d, 1H), 7.58 (d, 1H), 7.78 (d, 1H), 7.87 (m, 1H), 7.96 (s, 1H), 8.41 (d, 1H); Mass Spectrum: $M+H^+$ 432.

The 2-amino- *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-(4-methyl-1,4-diazepan-1-yl)benzamide used as starting material was prepared as follows :-

To a stirred solution of 4-methyl-3 nitrobenzoyl chloride (20 g) in methylene chloride (200 ml) at 0°C was added a mixture of cyclopropylamine (7.62 ml) and triethylamine (28 ml). The mixture was allowed to warm to room temperature and stirred for a further 16 hours. The reaction mixture was evaporated *in vacuo* and a saturated $NaHCO_3$ solution was added. The precipitated solid was filtered off and washed with *iso*-hexane and dried (magnesium sulphate) to give the title compound as a colourless solid (22.9 g); NMR Spectrum: ($DMSOd_6$) 0.60 (m, 2H), 0.72 (m, 2H), 2.56 (s, 3H), 2.87 (m, 1H), 7.60 (d, 1H), 8.06 (m, 1H), 8.41 (d, 1H), 8.67 (d, 1H); Mass Spectrum: $M+H^+$ 221.

A suspension of *N*-cyclopropyl-4-methyl-3-nitrobenzamide (22.92 g) and 10% palladium on carbon (2 g) in ethanol (500 ml) was agitated under a hydrogen atmosphere for 16 hours. The reaction mixture was filtered through diatomaceous earth (Celite®) and the filtrate evaporated to dryness to give the title compound as a colourless solid (17.1 g); NMR Spectrum: ($DMSOd_6$) 0.53 (m, 2H), 0.65 (m, 2H), 2.07 (s, 3H), 2.80 (m, 1H), 6.92 (m, 2H), 7.06 (d, 1H), 8.09 (d, 1H); Mass Spectrum: $M+H^+$ 191.

A) 3-amino-*N*-cyclopropyl-4-methylbenzamide (5.50 g) was added to a stirred solution of 5-chloro-2-nitrobenzoic acid (7.59 g), *N,N*-diisopropylethylamine (12.2 ml) and HATU (14.3 g) in DMF (50 ml). The mixture was stirred at room temperature for 16 hours. The reaction mixture was poured into a saturated $NaHCO_3$ solution (1000 ml) and the resulting solid was filtered and dried (magnesium sulphate) under vacuum at 40°C. There was thus obtained 5-chloro-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-2-nitrobenzamide (10.02 g); NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.67 (m, 2H), 2.30 (s, 3H), 2.83 (m, 1H), 7.31 (d, 1H), 7.61 (d, 1H), 7.85 (d, 1H), 7.93 (d, 2H), 8.18 (d, 1H), 8.37 (d, 1H); Mass Spectrum: $M+Na^+$ 396.

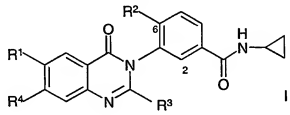
B) 1- Methylhomopiperazine (1.25 ml) was added to a stirred solution of 5-chloro-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-2-nitrobenzamide (0.6 g) in DMSO (5.0 ml). The mixture was heated to 80°C and stirred for 16 hours. The cooled mixture was poured into a saturated $NaHCO_3$ solution (100 ml) and extracted with ethyl acetate (100 ml) and methylene chloride (100 ml). The organic extracts were combined, dried (magnesium sulphate), concentrated under reduced pressure and the residue was triturated with ethyl acetate/*iso*-hexane. The resultant solid was filtered and dried under vacuum at 40°C. There was thus obtained *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-(4-methyl-1,4-diazepan-1-yl)-2-nitrobenzamide (0.34 g); NMR Spectrum: ($DMSOd_6$) 0.57 (m, 2H), 0.67 (m, 2H), 1.90 (m, 2H), 2.26 (s, 3H), 2.26 (s, 3H), 2.51 (m, 2H), 2.64 (m, 2H), 2.82 (m, 1H), 3.61 (t, 2H), 3.68 (t, 2H), 6.80 (d, 1H), 6.88 (d, 1H), 7.28 (d, 1H), 7.56 (d, 1H), 7.97 (s, 1H), 8.03 (d, 1H), 8.35 (d, 1H), 9.87 (s, 1H); Mass Spectrum: $M+H^+$ 452.

C) 10% Palladium-on-carbon (0.05 g) was added to a stirred suspension of *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-(4-methyl-1,4-diazepan-1-yl)-2-nitrobenzamide (0.304 g) in methanol (5 ml) and the mixture was stirred under an atmosphere of hydrogen gas at a pressure of 10 bar. After cessation of hydrogen uptake, the catalyst was removed by filtration through diatomaceous earth (Celite®). The filtrate was concentrated under reduced pressure, which provided the crude 2-amino-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-(4-methyl-1,4-diazepan-1-yl)benzamide (0.27 g) which was used without further purification; Mass Spectrum: $M+H^+$ 422.

Example 2

Using an analogous procedure to that described in Example 1, the appropriate starting material was reacted with triethylorthoformate to give the compounds described in Table 1.

Table 1



I

R^4	R^3	R^1	R^2	Method	Note
H	H	4-ethylpiperazin-1-yl	Me	Ex 1	a
H	H	4-isopropylpiperazin-1-yl	Me	Ex 1	b
H	H	(3S)-3-methylpiperazin-1-yl	Me	Ex 1	c
H	H	(3R)-3-methylpiperazin-1-yl	Me	Ex 1	d
H	H	4-(2-hydroxyethyl) piperazin-1-yl	Me	Ex 1	e
H	H	4-(*tert*-butylcarboxylate) piperazin-1-yl	Me	Ex 1	f
H	H	4-(tert-butylcarboxylate) 1,4-diazepan-1-yl	Me	Ex 1	g
H	H	4-methylpiperazin-1-yl	CF_3	Ex 1	h
H	H	4-[*tert*-butylacetyl]piperazin-1-yl	Me	Ex 1	i
H	H	(3S)-3,4-dimethylpiperazin-1-yl	Me	Ex 1	j
H	H	(3R)-3,4-dimethylpiperazin-1-yl	Me	Ex 1	k
H	H	4-(methylsulfonyl)piperazin-1-yl(AZ12203370)	Me	Ex 1	l
F	H	4-methylpiperazin-1-yl (AZ12263849)	Me	Ex 1	m
F	H	H (AZ12195830)	Me	Ex 1	n
MeO	H	H (AZ12280352)	Me	Ex 1	o
H	H	*tert*-butyl(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (AZ12264941)	Me	Ex 1	p

Notes

a) The product gave the following data; NMR Spectrum: (DMSOd_6) 0.54 (m, 2H), 0.68 (m, 2H), 1.02 (t, 3H), 2.11 (s, 3H), 2.37 (m, 2H), 2.51 (m, 4H), 2.84 (m, 1H), 3.25 (m, 4H), 7.45 (s, 1H), 7.50 (d, 1H), 7.62 (s, 2H), 7.80 (d, 1H), 7.88 (m, 1H), 8.06 (s, 1H), 8.41 (d, 1H); Mass Spectrum: M+H^+ 432.

The 2-amino- *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-(4-ethylpiperazin-1-yl)benzamide used for the starting material was prepared as follows:-

Using an analogous procedure to that described paragraph (B) in the portion of Example 1, which is concerned with the preparation of starting materials, *N*-ethylpiperazine was reacted with 5-chloro-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-2-nitrobenzamide to give *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-(4-ethylpiperazine-1-yl)-2-nitrobenzamide; NMR Spectrum: (DMSOd_6) 0.57 (m, 2H), 0.67 (m, 2H), 1.02 (t, 3H), 2.30 (s, 3H), 2.37 (m, 2H), 2.48 (m, 4H), 2.83 (m, 1H), 3.49 (m, 4H), 7.06 (m, 2H), 7.28 (d, 1H), 7.56 (d, 1H), 7.96 (s, 1H), 8.04 (d, 1H), 8.35 (d, 1H), 9.91 (s, 1H); Mass Spectrum: M+H^+ 452.

Using an analogous procedure to that described paragraph (C) in the portion of Example 1 which is concerned with the preparation of starting materials, *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-(4-ethylpiperazine-1-yl)-2-nitrobenzamide was reduced to give the required starting material; Mass Spectrum: M+H^+ 422.

b) The product gave the following data; NMR Spectrum (DMSOd_6): 0.54 (m, 2H), 0.67 (m, 2H), 0.99 (d, 6H), 2.11 (s, 3H), 2.59 (m, 4H), 2.67 (m, 1H), 2.83 (m, 1H), 3.25 (m, 4H), 7.44 (s, 1H), 7.50 (d, 1H), 7.61 (s, 2H), 7.79 (d, 1H), 7.88 (m, 1H), 8.06 (s, 1H), 8.41 (d, 1H); Mass Spectrum: M+H^+ 446.

The 2-amino- *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-(4-isopropylpiperazin-1-yl)benzamide used as a starting material was prepared as follows:-

Using an analogous procedure to that described paragraph (B) in the portion of Example 1 which is concerned with the preparation of starting materials, *N*-isopropylpiperazine was reacted with 5-chloro-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-2-nitrobenzamide to give *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-(4-isopropylpiperazine-1-yl)-2-nitrobenzamide; NMR Spectrum: (DMSOd_6) 0.57 (m, 2H), 0.67 (m, 2H), 0.99 (d, 6H), 2.29 (s, 3H), 2.54 (m, 4H), 2.68 (m, 1H), 2.83 (m,

1H), 3.48 (m, 4H), 7.05 (m, 2H), 7.27 (d, 1H), 7.56 (d, 1H), 7.96 (s, 1H), 8.03 (d, 1H), 8.35 (d, 1H), 9.90 (s, 1H); Mass Spectrum $M+H^+$ 466.

Using an analogous procedure to that described paragraph (C) in the portion of Example 1 which is concerned with the preparation of starting materials, *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-(4-isopropylpiperazine-1-yl)-2-nitrobenzamide was reduced to give the required starting material; Mass Spectrum: $M+H^+$ 436.

c) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.53 (m, 2H), 0.65 (m, 2H), 1.03 (m, 3H), 2.11 (s, 3H), 2.28 (t, 1H), 2.64 (t, 1H), 2.80 (m, 3H), 2.98 (d, 1H), 3.64 (m, 2H), 7.43 (s, 1H), 7.50 (d, 1H), 7.61 (s, 2H), 7.79 (s, 1H), 7.87 (d, 1H), 8.05 (s, 1H), 8.41 (d, 1H); Mass Spectrum: $M+H^+$ 418.

The 2-amino-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-[(3S)-3-methylpiperazin-1-yl)benzamide used for the starting material was prepared as follows:-

Using an analogous procedure to that described paragraph (B) in the portion of Example 1 which is concerned with the preparation of starting material (S)-2-methylpiperazine was reacted with 5-chloro-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-2-nitrobenzamide to give *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-[(3S)-3-methylpiperazine-1-yl)-2-nitrobenzamide; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.67 (m, 2H), 1.05 (d, 3H), 2.29 (s, 3H), 2.53 (m, 2H), 2.79 (m, 4H), 3.00 (d, 1H), 3.93 (t, 2H), 7.05 (m, 2H), 7.27 (d, 1H), 7.56 (d, 1H), 7.97 (s, 1H), 8.03 (d, 1H), 8.35 (d, 1H), 9.88 (s, 1H); Mass Spectrum: $M+H^+$ 438.

Using an analogous procedure to that described paragraph (C) in the portion of Example 1 which is concerned with the preparation of starting materials, *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-[(3S)-3-methylpiperazine-1-yl)-2-nitrobenzamide was reduced to give the required starting material; Mass Spectrum: $M+H^+$ 408.

d) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.53 (m, 2H), 0.66 (m, 2H), 1.04 (d, 3H), 2.11 (s, 3H), 2.31 (t, 1H), 2.66 (m, 1H), 2.81 (m, 3H), 3.00 (d, 1H), 3.66 (m, 2H), 7.44 (s, 1H), 7.50 (d, 1H), 7.61 (s, 2H), 7.61 (s, 1H), 7.88 (d, 1H), 8.06 (s, 1H), 8.41 (d, 1H); Mass Spectrum: $M+H^+$ 418.

The 2-amino-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-[(3R)-3-methylpiperazin-1-yl)benzamide used for the starting material was prepared as follows:-

Using an analogous procedure to that described paragraph (B) in the portion of Example 1 which is concerned with the preparation of starting material (R)-2-methylpiperazine was reacted with 5-chloro-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-2-nitrobenzamide to give *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-[(3R)-3-methylpiperazine-1-yl)-2-nitrobenzamide; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.67 (m, 2H), 1.04 (d, 3H), 2.30 (s, 3H), 2.52 (m, 2H), 2.71 (m, 2H), 2.84 (m, 2H), 2.98 (d, 1H), 3.92 (t, 2H), 7.04 (m, 2H), 7.27 (d, 1H), 7.56 (d, 1H), 7.97 (s, 1H), 8.03 (d, 2H), 8.35 (d, 1H), 9.88 (s, 1H); Mass Spectrum: $M+H^+$ 438.

Using an analogous procedure to that described paragraph (C) in the portion of Example 1 which is concerned with the preparation of starting materials, *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-[(3R)-3-methylpiperazine-1-yl)-2-nitrobenzamide was reduced to give the required starting material; Mass Spectrum: $M+H^+$ 408.

e) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.54 (m, 2H), 0.68 (m, 2H), 2.11 (s, 3H), 2.43 (m, 2H), 2.57 (m, 4H), 2.83 (m, 1H), 3.26 (m, 4H), 3.52 (m, 2H), 4.40 (m, 1H), 7.45 (s, 1H), 7.50 (d, 1H), 7.62 (s, 2H), 7.62 (s, 1H), 7.87 (d, 1H), 8.06 (s, 1H), 8.41 (d, 1H); Mass Spectrum: $M+H^+$ 448.

The 2-amino-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-[4-(2-hydroxyethyl)piperazin-1-yl)benzamide used for the starting material was prepared as follows:-

Using an analogous procedure to that described paragraph (B) in the portion of Example 1 which is concerned with the preparation of starting materials, *N*-piperazine ethanol was reacted with 5-chloro-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-2-nitrobenzamide to give *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-[4-(2-hydroxyethyl)piperazine-1-yl)-2-nitrobenzamide; NMR Spectrum: ($DMSOd_6$) 0.57 (m, 2H), 0.68 (m, 2H), 2.30 (s, 3H), 2.44 (t, 2H), 2.54 (m, 4H), 2.83 (m, 1H), 3.50 (m, 6H), 4.46 (s, 1H), 7.05 (m, 2H), 7.28 (d, 1H), 7.56 (d, 1H), 7.96 (s, 1H), 8.04 (d, 1H), 8.35 (d, 1H), 9.90 (s, 1H); Mass Spectrum: $M+H^+$ 468.

Using an analogous procedure to that described paragraph (C) in the portion of Example 1 which is concerned with the preparation of starting materials, *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-[4-(2-hydroxyethyl)piperazine-1-yl)-

2-nitrobenzamide was reduced to give the required starting material; Mass Spectrum: $M+H^+$ 438.

f) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.55 (m, 3H), 0.69 (m, 3H), 1.42 (s, 16H), 2.12 (s, 4H), 2.85 (m, 2H), 3.28 (m, 9H), 3.47 (m, 8H), 7.51 (m, 3H), 7.64 (m, 3H), 7.79 (m, 2H), 7.89 (m, 2H), 8.09 (s, 1H), 8.42 (m, 1H); Mass Spectrum: $M+H^+$ 504.

The *tert*-butyl 4-{4-amino-3-[({5-[(cyclopropylamino)carbonyl]-2-methylphenyl}amino)carbonyl]phenyl}piperazine-1-carboxylate used for the starting material was prepared as follows:-

Using an analogous procedure to that described paragraph (A) in the portion of Example 1 which is concerned with the preparation of starting materials, 3-amino-*N*-cyclopropyl-4-methylbenzamide was reacted with 5-fluoro-2-nitrobenzoic acid to give 5-fluoro-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-2-nitrobenzamide; NMR Spectrum: ($DMSOd_6$) 0.58 (m, 2H), 0.69 (m, 2H), 2.30 (s, 3H), 2.85 (m, 1H), 7.31 (m, 1H), 7.61 (m, 2H), 7.76 (m, 1H), 7.94 (s, 1H), 8.26 (m, 1H), 8.40 (m, 1H), 10.25 (s, 1H); Mass Spectrum: $M-H^+$ 356.

Using an analogous procedure to that described paragraph (B) in the portion of Example 1 which is concerned with the preparation of starting material *tert*-butyl-piperazine-1-carboxylate was reacted with 5-fluoro-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-2-nitrobenzamide to *tert*-butyl 4-{3-[({5-[(cyclopropylamino)carbonyl]-2-methylphenyl}amino)carbonyl]-4-nitrophenyl}piperazine-1-carboxylate; NMR Spectrum: ($DMSOd_6$) 0.58 (m, 2H), 0.68 (m, 2H), 1.40 (s, 9H), 2.30 (s, 3H), 2.85 (m, 1H), 3.50 (m, 8H), 7.06 (m, 2H), 7.29 (d, 1H), 7.57 (m, 1H), 7.94 (m, 1H), 8.07 (m, 1H), 8.37 (d, 1H), 9.93 (s, 1H); Mass Spectrum: $M-H^+$ 522.

Using an analogous procedure to that described paragraph (C) in the portion of Example 1 which is concerned with the preparation of starting materials, *tert*-butyl 4-{3-[({5-[(cyclopropylamino)carbonyl]-2-methylphenyl}amino)carbonyl]-4-nitrophenyl}piperazine-1-carboxylate was reduced to give the required starting material; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.68 (m, 2H), 1.40 (s, 9H), 2.25 (s, 3H), 2.85 (m, 1H), 2.97 (m, 4H), 3.46 (m, 4H), 6.00 (s, 2H), 6.70 (m, 1H), 6.99 (m, 1H), 7.30 (m, 2H), 7.62 (m, 1H), 7.75 (m, 1H), 8.36 (m, 1H), 9.74 (s, 1H); Mass Spectrum: $M+H^+$ 494.

g) The product gave the following data; NMR Spectrum: ($DMSOd_6$ at 373K) 0.55 (m, 2H), 0.69 (m, 2H), 1.27 (s, 9H), 1.82 (t, 2H), 2.11 (s, 3H), 2.85 (m, 1H), 3.20 (t, 2H), 3.61 (m, 6H), 7.27 (s, 1H), 7.40 (m, 1H), 7.51 (d, 1H), 7.59 (d, 1H), 7.78 (s, 1H), 7.88 (d, 1H), 7.96 (s, 1H), 8.42 (s, 1H); Mass Spectrum: $M+H^+$ 518.

The *tert*-butyl 4-{4-amino-3-[({5-[(cyclopropylamino)carbonyl]-2-methylphenyl}amino)carbonyl]phenyl}-1,4-diazepane-1-carboxylate used for the starting material was prepared as follows:-

Using an analogous procedure to that described paragraph (B) in the portion of Example 1 which is concerned with the preparation of starting material *tert*-butyl-1,4-diazepane-1-carboxylate was reacted with 5-fluoro-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-2-nitrobenzamide to *tert*-butyl 4-{3-[({5-[(cyclopropylamino)carbonyl]-2-methylphenyl}amino)carbonyl]-4-nitrophenyl}-1,4-diazepane-1-carboxylate; NMR Spectrum: ($DMSOd_6$) 0.59 (m, 2H), 0.70 (m, 2H), 1.33 (s, 9H), 1.74 (m, 2H), 2.30 (s, 3H), 2.85 (m, 1H), 3.65 (m, 8H), 6.91 (m, 2H), 7.25 (m, 1H), 7.57 (m, 1H), 7.99 (m, 2H), 8.37 (m, 1H), 9.82 (d, 1H); Mass Spectrum: $M-H^+$ 536.

Using an analogous procedure to that described paragraph (C) in the portion of Example 1 which is concerned with the preparation of starting materials, *tert*-butyl 4-{3-[({5-[(cyclopropylamino)carbonyl]-2-methylphenyl}amino)carbonyl]-4-nitrophenyl}-1,4-diazepane-1-carboxylate was reduced to give the required starting material; NMR Spectrum: ($DMSOd_6$) 0.57 (m, 2H), 0.66 (m, 2H), 1.33 (s, 9H), 1.81 (m, 2H), 2.26 (m, 3H), 2.81 (m, 1H), 3.38 (m, 8H), 5.62 (s, 2H), 6.67 (m, 1H), 6.82 (m, 1H), 7.02 (m, 1H), 7.31 (d, 1H), 7.60 (d, 1H), 7.84 (d, 1H), 8.36 (d, 1H), 9.72 (d, 1H); Mass Spectrum: $M+H^+$ 508.

h) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 3H), 0.85 (m, 2H), 2.37 (s, 4H), 2.61 (m, 6H), 2.78 (m, 1H), 3.35 (m, 5H), 6.79 (s, 1H), 7.39 (m, 1H), 7.47 (s, 1H), 7.62 (d, 1H), 7.74 (s, 1H), 7.85 (m, 3H), 8.07 (m, 1H); Mass Spectrum: $M-H^+$ 470.

The 2-amino-*N*-[5-[(cyclopropylamino)carbonyl]-2-(trifluoromethyl)phenyl]-5-(4-methylpiperazin-1-yl)benzamide used for the starting material was prepared as follows:-

To a stirred solution of 3-nitro-4-(trifluoromethyl)benzoic acid (9.4 g) in methylene chloride (80 ml) at 0°C was added oxalyl chloride (7 ml) dropwise followed by DMF (1 drop). The reaction was warmed to room temperature and stirred for 4 hours. The solvent was evaporated *in vacuo*. The residue was resuspended in methylene chloride (80 ml) and a

mixture of cyclopropylamine (3.3 ml) and diisopropylethylamine (16.7 ml) was added. The mixture was allowed to warm to room temperature and stirred for 90 minutes. The reaction mixture was evaporated. 2N HCl (200 ml) added to the residue and extracted ethyl acetate (3 x 200 ml). The organic phases were combined, washed with 2N HCl (2 x 150 ml), saturated $NaHCO_3$ solution (3 x 100 ml), brine (100 ml) and then dried (magnesium sulphate) and evaporated *in vacuo* to give the title compound (10.85g); NMR Spectrum: ($DMSOd_6$) 0.60 (m, 2H), 0.72 (m, 2H), 2.89 (m, 1H), 8.14 (m, 1H), 8.29 (m, 1H), 8.49 (s, 1H), 8.88 (m, 1H); Mass Spectrum: $M+H^+$ 275.

A suspension of *N*-cyclopropyl-3-nitro-4-(trifluoromethyl)benzamide (22.92 g) and 10% palladium on carbon (2 g) in ethanol (500 ml) was agitated under a hydrogen atmosphere for 16 hours. The reaction mixture was filtered through diatomaceous earth (Celite®) and the filtrate evaporated to dryness to give the title compound as a colourless solid (17.1 g); NMR Spectrum: ($DMSOd_6$) 0.52 (m, 2H), 0.67 (m, 2H), 2.79 (m, 1H), 5.70 (s, 2H), 6.96 (d, 1H), 7.23 (s, 1H), 7.36 (m, 1H), 8.37 (m, 1H); Mass Spectrum: $M+H^+$ 245.

Using an analogous procedure to that described paragraph (A) in the portion of Example 1 which is concerned with the preparation of starting materials, 3-amino-*N*-cyclopropyl-4-(trifluoromethyl)benzamide was reacted with 5-fluoro-2-nitrobenzoic acid to give *N*-[5-[(cyclopropylamino)carbonyl]-2-(trifluoromethyl)phenyl]-5-fluoro-2-nitrobenzamide; Mass Spectrum: $M-H^+$ 410.

Using an analogous procedure to that described paragraph (B) in the portion of Example 1 which is concerned with the preparation of starting material, *N*-methylpiperazine was reacted with *N*-[5-[(cyclopropylamino)carbonyl]-2-(trifluoromethyl)phenyl]-5-fluoro-2-nitrobenzamide to *N*-[5-[(cyclopropylamino)carbonyl]-2-(trifluoromethyl)phenyl]-5-(4-methylpiperazin-1-yl)-2-nitrobenzamide; NMR Spectrum: ($DMSOd_6$) 0.58 (m, 2H), 0.70 (m, 2H), 2.23 (s, 3H), 2.45 (m, 4H), 2.89 (m, 1H), 3.47 (m, 4H), 6.89 (s, 1H), 7.11 (d, 1H), 7.87 (s, 2H), 8.06 (m, 2H), 8.78 (m, 1H), 10.28 (s, 1H); Mass Spectrum: $M-H^+$ 491.

Using an analogous procedure to that described paragraph (C) in the portion of Example 1 which is concerned with the preparation of starting materials, *N*-[5-[(cyclopropylamino)carbonyl]-2-(trifluoromethyl)phenyl]-5-(4-methylpiperazin-1-yl)-2-nitrobenzamide was reduced to give the required starting material; Mass Spectrum: $M+H^+$ 462.

i) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.55 (m, 2H), 0.68 (m, 2H), 1.42 (s, 9H), 2.12 (s, 3H), 2.69 (m, 4H), 2.85 (m, 1H), 3.17 (m, 2H), 3.28 (m, 4H), 7.50 (m, 2H), 7.62 (m, 2H), 7.81 (m, 1H), 7.88 (m, 1H), 8.07 (s, 1H), 8.42 (d, 1H); Mass Spectrum: $M+H^+$ 518.

The *tert*-butyl (4-{4-amino-3-[({5-[(cyclopropylamino)carbonyl]-2-methylphenyl}amino)carbonyl]phenyl}piperazin-1-yl)acetate used for the starting material was prepared as follows:-

Using an analogous procedure to that described paragraph (B) in the portion of Example 1 which is concerned with the preparation of starting materials, *tert*-butyl piperazin-1-ylacetate was reacted with *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-fluoro-2-nitrobenzamide to give *tert*-butyl (4-{3-[({5-[(cyclopropylamino)carbonyl]-2-methylphenyl}amino)carbonyl]-4-nitrophenyl}piperazin-1-yl)acetate; NMR Spectrum: ($DMSOd_6$) 0.58 (m, 2H), 0.70 (m, 2H), 1.43 (s, 9H), 2.32 (s, 3H), 2.66 (m, 4H), 2.86 (m, 1H), 3.21 (s, 2H), 3.53 (m, 4H), 7.09 (m, 2H), 7.30 (m, 1H), 7.59 (m, 1H), 7.99 (s, 1H), 8.07 (m, 1H), 8.38 (m, 1H), 9.93 (s, 1H); Mass Spectrum: $M+H^+$ 538.

Using an analogous procedure to that described paragraph (C) in the portion of Example 1 which is concerned with the preparation of starting materials, *tert*-butyl (4-{3-[({5-[(cyclopropylamino)carbonyl]-2-methylphenyl}amino)carbonyl]-4-nitrophenyl}piperazin-1-yl)acetate was reduced to give the required starting material; Mass Spectrum: $M-H^+$ 506.

j) The product gave the following data: NMR Spectrum: ($DMSOd_6$) 0.53 (m, 2H), 0.67 (m, 2H), 1.04 (d, 3H), 2.13 (m, 9H), 2.85 (m, 3H), 3.66 (m, 2H), 7.45 (s, 1H), 7.51 (d, 1H), 7.61 (s, 2H), 7.81 (s, 1H), 7.87 (d, 1H), 8.06 (s, 1H), 8.42 (d, 1H); Mass Spectrum: $M+H^+$ 432.

The 2-amino-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-[(3S)-3,4-dimethylpiperazin-1-yl]benzamide used for the starting material was prepared as follows:-

Using an analogous procedure to that described paragraph (B) in the portion of Example 1 which is concerned with the preparation of starting material (S)-2-methylpiperazine was reacted with 5-chloro-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-2-nitrobenzamide to give *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-[(3S)-3-methylpiperazine-1-yl)-2-nitrobenzamide; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.67 (m, 2H), 1.05 (d, 3H), 2.29 (s, 3H), 2.53 (m, 2H), 2.79 (m, 4H), 3.00 (d, 1H), 3.93 (t, 2H), 7.05 (m, 2H), 7.27 (d, 1H), 7.56 (d, 1H), 7.97 (s, 1H), 8.03 (d, 1H), 8.35 (d, 1H), 9.88 (s, 1H); Mass Spectrum: $M+H^+$ 438.

1-Iodomethane (0.081 ml) was added to a stirred mixture of *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-[(3S)-3-methylpiperazine-1-yl)-2-nitrobenzamide (0.517 g) and potassium carbonate (0.686 g) in DMA (1.50 ml). The mixture was stirred at room ternperature for 16 hours. The reaction mixture was poured into water (15 ml) and the resulting solid was filtered and dried under vacuum at 40°C. There was thus obtained *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-[(3S)-3,4-dimethylpiperazine-1-yl)-2-nitrobenzamide (0.365 g); NMR Spectrum: 0.56 (m, 2H), 0.67 (m, 2H), 1.06 (d, 3H), 2.09 (m, 2H), 2.20 (s, 3H), 2.30 (s, 3H), 2.68 (m, 1H), 2.83 (m, 2H), 3.04 (m, 1H), 3.92 (m, 2H), 7.05 (m, 2H), 7.28 (d, 1H), 7.56 (d, 1H), 7.97 (s, 1H), 8.03 (d, 1H), 8.36 (d, 1H), 9.89 (s, 1H); Mass Spectrum: $M+H^+$ 452.

Using an analogous procedure to that described paragraph (C) in the portion of Example 1 which is concerned with the preparation of starting materials, *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-[(3S)-3,4-dimethylpiperazine-1-yl)-2-nitrobenzamide was reduced to give the required starting material; Mass Spectrum $M+H^+$ 422.

k) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.53 (m, 2H), 0.66 (m, 2H), 1.06 (d, 3H), 2.16 (m, 9H), 2.84 (m, 3H), 3.66 (m, 2H), 7.45 (s, 1H), 7.50 (d, 1H), 7.62 (s, 2H), 7.81 (s, 1H), 7.87 (d, 1H), 8.06 (s, 1H), 8.41 (d, 1H); Mass Spectrum: $M+H^+$ 432.

The 2-amino- *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-[(3R)-3,4-dimethylpiperazin-1-yl]benzamide used for the starting material was prepared as follows:-

Using an analogous procedure to that described paragraph (B) in the portion of Example 1 which is concerned with the preparation of starting material (R)-2-methylpiperazine was reacted with 5-chloro-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-2-nitrobenzamide to give *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-[(3R)-3-methylpiperazine-1-yl)-2-nitrobenzamide; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.67 (m, 2H), 1.04 (d, 3H), 2.30 (s, 3H), 2.52 (m, 2H), 2.71 (m, 2H), 2.84 (m, 2H), 2.98 (d, 1H), 3.92 (t, 2H), 7.04 (m, 2H), 7.27 (d, 1H), 7.56 (d, 1H), 7.97 (s, 1H), 8.03 (d, 2H), 8.35 (d, 1H), 9.88 (s, 1H); Mass Spectrum: $M+H^+$ 438.

1-Iodomethane (0.050 ml) was added to a stirred mixture of *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-[(3R)-3-methylpiperazine-1-yl)-2-nitrobenzamide (0.32 g) and potassium carbonate (0.43 g) in DMA (1.5 ml). The mixture was stirred at room temperature for 16 hours. The reaction mixture was poured into water (15 ml)

and the resulting solid was filtered and dried under vacuum at 40°C. There was thus obtained *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-[(3R)-3,4-dimethylpiperazine-1-yl)-2-nitrobenzamide (0.21 g); NMR Spectrum: 0.55 (m, 2H), 0.66 (m, 2H), 1.05 (d, 3H), 2.10 (m, 2H), 2.20 (s, 3H), 2.29 (s, 3H), 2.68 (m, 1H), 2.83 (m, 2H), 3.05 (m, 1H), 3.93 (m, 2H), 7.05 (m, 2H), 7.28 (d, 1H), 7.56 (d, 1H), 7.98 (s, 1H), 8.03 (d, 1H), 8.36 (d, 1H), 9.89 (s, 1H); Mass Spectrum: $M+H^+$ 452.

Using an analogous procedure to that described paragraph (C) in the portion of Example 1 which is concerned with the preparation of starting materials, *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-[(3R)-3,4-dimethylpiperazine-1-yl)-2-nitrobenzamide was reduced to give the required starting material; Mass Spectrum: $M+H^+$ 422.

l) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.62 (m, 4H), 2.12 (s, 3H), 2.84 (m, 1H), 2.92 (s, 3H), 3.28 (m, 4H), 3.42 (m, 4H), 7.51 (m, 2H), 7.66 (m, 2H), 7.81 (d, 1H), 7.89 (m, 1H), 8.10 (d, 1H), 8.42 (d, 1H); Mass Spectrum: $M+Na^+$ 504.

The 2-amino-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-[4-(methylsulfonyl)piperazin-1-yl]benzamide used for the starting material was prepared as follows:-

Using an analogous procedure to that described paragraph (B) in the portion of Example 1 which is concerned with the preparation of starting materials, 1-(methylsulfonyl)piperazine was reacted with *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-fluoro-2-nitrobenzamide to give *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-[4-(methylsulfonyl)piperazin-1-yl]-2-nitrobenzamide; NMR Spectrum: ($DMSOd_6$) 0.64 (m, 4H), 2.31 (s, 3H), 2.84 (m, 1H), 2.93 (s, 3H), 3.26 (m, 4H), 3.64 (m, 4H), 7.13 (m, 2H), 7.29 (d, 1H), 7.58 (d, 1H), 7.98 (s, 1H), 8.08 (t, 1H), 8.37 (d, 1H), 9.95 (s, 1H); Mass Spectrum: $M-H^+$ 500.

Using an analogous procedure to that described paragraph (C) in the portion of Example 1 which is concerned with the preparation of starting materials, *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-[4-(methylsulfonyl)piperazin-1-yl]-2-nitrobenzamide was reduced to give the required starting material; Mass Spectrum: $M+H^+$ 472.

m) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.73 (s, 4H), 2.12 (s, 3H), 2.23 (s, 3H), 2.55 (m, 4H), 2.84 (m, 1H), 3.20 (m, 4H), 7.51 (m, 1H), 7.56 (m, 1H), 7.64

(d, 1H), 7.81 (d, 1H), 7.89 (m, 1H), 8.21 (s, 1H), 8.41 (d, 1H); Mass Spectrum: M+Na$^+$ 436.

The 2-amino-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4-fluoro-5-(4-methylpiperazin-1-yl)benzamide used for the starting material was prepared as follows:-

Using an analogous procedure to that described paragraph (A) in the portion of Example 1 which is concerned with the preparation of starting materials, 3-amino-*N*-cyclopropyl-4-methylbenzamide was reacted with 4,5-difluoro-2-nitrobenzoic acid to *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4,5-difluoro-2-nitrobenzamide; NMR Spectrum: (DMSOd_6) 0.63 (d, 4H), 2.29 (s, 3H), 2.84 (m, 1H), 7.31 (d, 1H), 7.62 (m, 1H), 7.93 (d, 1H), 8.12 (m, 1H), 8.42 (m, 2H), 10.31 (s, 1H); Mass Spectrum: M-H$^+$ 374.

Using an analogous procedure to that described paragraph (B) in the portion of Example 1 which is concerned with the preparation of starting materials, *N*-methylpiperazine was reacted with *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4,5-difluoro-2-nitrobenzamide to *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4-fluoro-5-(4-methylpiperazin-1-yl)-2-nitrobenzamide; NMR Spectrum: (DMSOd_6) 0.73 (s, 4H), 2.23 (s, 3H), 2.30 (s, 3H), 2.48 (d, 4H), 2.75 (m, 1H), 3.35 (m, 4H), 7.21 (d, 1H), 7.30 (d, 1H), 7.61 (m, 1H), 8.06 (m, 2H), 8.38 (d, 1H), 10.00 (s, 1H); Mass Spectrum: M+H$^+$ 456.

Using an analogous procedure to that described paragraph (C) in the portion of Example 1 which is concerned with the preparation of starting materials, *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4-fluoro-5-(4-methylpiperazin-1-yl)-2-nitrobenzamide was reduced to give the required starting material; NMR Spectrum: (DMSOd_6) 0.61 (m, 4H), 2.22 (s, 3H), 2.23 (s, 3H), 2.45 (m, 4H), 2.79 (m, 1H), 2.92 (m, 2H), 3.50 (m, 2H), 6.36 (s, 2H), 6.52 (d, 1H), 7.31 (d, 1H), 7.38 (d, 1H), 7.62 (m, 1H), 7.73 (m, 1H), 8.35 (d, 1H), 9.72 (s, 1H); Mass Spectrum: M+H$^+$ 426.

n) The product gave the following data; NMR Spectrum: (DMSOd_6) 0.62 (m, 2H), 0.76 (m, 2H), 2.21 (s, 3H), 2.91 (m, 1H), 7.57 (m, 2H), 7.66 (m, 1H), 7.92 (d, 1H), 7.97 (m, 1H), 8.34 (m, 1H), 8.44 (s, 1H), 8.53 (d, 1H); Mass Spectrum: M+H$^+$ 338.

The 2-amino-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4-fluorobenzamide used as starting material was prepared as follows :-

To a stirred solution of 3-amino-*N*-cyclopropyl-4-methylbenzamide (2.85 g) and 4-fluoro-2-nitrobenzoic acid (4.21 g) in dimethylformamide (30 ml) at room temperature was added a mixture of HATU (6.86 g) and pyridine (3 ml). The mixture was stirred at room temperature for a further 16 hours. The reaction mixture was evaporated. The residue was

partitioned between methylene chloride and saturated $NaHCO_3$ solution. The resulting aqueous extract was extracted with methylene chloride. The combined organic extracts were washed with water. The precipitated solid was filtered off and the organic phase dried (magnesium sulphate) and evaporated. The combined solids were triturated with diethyl ether to give the title compound as a solid (3.84 g); NMR Spectrum: ($DMSOd_6$) 0.59 (m, 2H), 0.69 (m, 2H), 2.30 (s, 3H), 2.85 (m, 1H), 7.32 (d, 1H), 7.62 (d, 1H), 7.78 (m, 1H), 7.93 (m, 2H), 8.09 (m, 1H), 8.45 (s, 1H), 10.42 (s, 1H); Mass Spectrum: $M+H^+$ 358.

A suspension of *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4-fluoro-2-nitrobenzamide (0.49 g) and 10% palladium on carbon (0.05 g) in ethanol (40 ml) was agitated under a hydrogen atmosphere for 16 hours. The reaction mixture was filtered through diatomaceous earth (Celite®) and the filtrate evaporated to dryness to give the title compound as a solid (0.57 g); NMR Spectrum: ($DMSOd_6$) 0.57 (m, 2H), 0.68 (m, 2H), 2.25 (s, 3H), 2.85 (m, 1H), 6.39 (m, 1H), 6.52 (m, 1H), 6.75 (s, 2H), 7.32 (d, 1H), 7.63 (m, 1H), 7.80 (m, 2H), 8.41 (d, 1H), 9.79 (s, 1H); Mass Spectrum: $M+H^+$ 328.

o) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.57 (m, 2H), 0.70 (m, 2H), 2.15 (s, 3H), 2.87 (m, 1H), 3.95 (s, 3H), 7.21 (m, 2H), 7.53 (d, 1H), 7.84 (s, 1H), 7.90 (m, 1H), 8.12 (d, 1H), 8.28 (s, 1H), 8.43 (d, 1H); Mass Spectrum: $M+H^+$ 350.

The 2-amino-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4-methoxybenzamide used as starting material was prepared as follows:-

To a stirred solution of 3-amino-*N*-cyclopropyl-4-methylbenzamide (1.47 g) and 4-methoxy-2-nitrobenzoic acid (2.00 g) in DMF (20 ml) at room temperature was added a mixture of HATU (3.55 g) and pyridine (1.5 ml). The mixture was stirred at room temperature for a further 16 hours. The reaction mixture was evaporated. The residue was partitioned between methylene chloride and saturated $NaHCO_3$ solution. The resulting aqueous extract was extracted with methylene chloride. The precipitated solid was filtered off to give the title compound as a solid (2.86 g); NMR Spectrum: ($DMSOd_6$) 0.59 (m, 2H), 0.70 (m, 2H), 2.51 (s, 3H), 2.85 (m, 1H), 3.93 (s, 3H), 7.32 (d, 1H), 7.41 (m, 1H), 7.62 (m, 2H), 7.78 (d, 1H), 7.87 (s, 1H), 8.40 (s, 1H), 10.15 (s, 1H); Mass Spectrum: $M+H^+$ 370.

A suspension of *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4-methoxy-2-nitrobenzamide (2.00 g) and 10% palladium on carbon (0.21 g) in ethanol (100 ml) was agitated under a hydrogen atmosphere for 16 hours. The reaction mixture was filtered through diatomaceous earth (Celite®) and the filtrate evaporated to dryness to give the title compound

as a solid (1.81 g); NMR Spectrum: ($DMSOd_6$) 0.57 (m, 2H), 0.69 (m, 2H), 2.25 (s, 3H), 2.85 (m, 1H), 3.74 (s, 3H), 6.19 (m, 1H), 6.29 (d, 1H), 6.61 (s, 2H), 7.31 (d, 1H), 7.61 (m, 1H), 7.71 (d, 1H), 7.76 (d, 1H), 8.36 (d, 1H), 9.51 (s, 1H); Mass Spectrum: $M+H^+$ 340.

p) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.70 (m, 2H), 1.37 (d, 9H), 1.97 (m, 2H), 2.14 (m, 3H), 2.86 (m, 1H), 3.11 (m, 1H), 3.23 (m, 1H), 3.38 (m, 1H), 3.67 (m, 1H), 4.49 (d, 1H), 4.70 (m, 1H), 7.15 (t, 1H), 7.30 (m, 1H), 7.52 (d, 1H), 7.63 (d, 1H), 7.81 (m, 1H), 7.90 (m, 1H), 8.01 (s, 1H), 8.42 (m, 1H); Mass Spectrum: $M+H^+$ 516.

The *tert*-butyl(1*S*,4*S*)-5-{4-amino-3-[({5-[(cyclopropylamino)carbonyl]-2-methylphenyl}amino)carbonyl]phenyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate used as starting material was prepared as follows :-

Using an analogous procedure to that described paragraph (B) in the portion of Example 1, which is concerned with the preparation of starting materials, and *tert*-butyl(1*S*,4*S*)-(-)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate was reacted with *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-fluoro-2-nitrobenzamide to give of *tert*-butyl(1*S*,4*S*)-5-{3-[({5-[(cyclopropylamino)carbonyl]-2-methylphenyl}amino)carbonyl]-4-nitrophenyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate; NMR Spectrum: ($DMSOd_6$) 0.59 (m, 2H), 0.70 (m, 2H), 1.39 (d, 9H), 2.00 (m, 2H), 2.32 (s, 3H), 2.54 (s, 2H), 2.86 (m, 1H), 3.40 (m, 1H), 3.66 (t, 1H), 4.53 (d, 1H), 4.87 (s, 1H), 6.80 (s, 2H), 7.30 (d, 1H), 7.58 (m, 1H), 8.01 (s, 1H), 8.07 (d, 1H), 8.38 (d, 1H), 9.90 (s, 1H); Mass Spectrum: $M+H^+$ 536.

Using an analogous procedure to that described paragraph (C) in the portion of Example 1, which is concerned with the preparation of starting materials, *tert*-butyl(1*S*,4*S*)-5-{3-[({5-[(cyclopropylamino)carbonyl]-2-methylphenyl}amino)carbonyl]-4-nitrophenyl}-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate was reduced to give the required starting material; NMR Spectrum: ($DMSOd_6$) 0.58 (m, 2H), 0.69 (m, 2H), 1.37 (d, 9H), 1.88 (m, 2H), 2.26 (s, 3H), 2.86 (m, 1H), 2.99 (m, 1H), 3.45 (m, 2H), 3.53 (m, 1H), 4.43 (s, 2H), 5.68 (s, 2H), 6.70 (m, 2H), 6.92 (s, 1H), 7.33 (d, 1H), 7.63 (m, 1H), 7.82 (s, 1H), 8.37 (d, 1H), 9.76 (s, 1H); Mass Spectrum: $M+H^+$ 506.

Example 3

[4-(3-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4-oxo-3,4-dihydroquinazolin-6-yl)piperazin-1-yl]acetic acid (AZ12189157)

To a stirred solution of *tert*-butyl-[4-(3-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4-oxo-3,4-dihydroquinazolin-6-yl)piperazin-1-yl]acetate (0.28 g) in methylene chloride (10 ml) was added 4N HCl in dioxane (3 ml). After 72 hours water (15 ml) was added and the solution poured onto an ion exchange column (isolute SCX-2 column from International Sorbent Technology Limited, Henoed, Mid-Glamorgan, UK). The column was washed with water (2 x 50 ml), methanol (2 x 50 ml) and the product eluted with 2N ammonia in methanol. The fractions containing product were evaporated *in vacuo*, triuration with *iso*-hexane/ethyl acetate gave the title compound (0.21 g); NMR Spectrum: ($DMSOd_6$) 0.61 (m, 4H), 2.12 (s, 3H), 2.70 (m, 4H), 2.84 (m, 1H), 3.09 (s, 2H), 3.28 (m, 4H), 7.49 (m, 2H), 7.62 (m, 2H), 7.81 (d, 1H), 7.89 (m, 1H), 8.07 (s, 1H), 8.44 (d, 1H); Mass Spectrum: $M+H^+$ 462.

Example 4

***N*-Cyclopropyl-4-methyl-3-[6-[(1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl]-4-oxoquinazolin-3(4*H*)-yl]benzamide (AZ12265665)**

A solution of *tert*-butyl(1*S*,4*S*)-5-(3-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4-oxo-3,4-dihydroquinazolin-6-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (0.30 g) and 38% aqueous formaldehyde (0.42 ml) in formic acid (5 ml) was stirred at 90°C for 16 hours. The reaction mixture was diluted with water and sodium bicarbonate added, evacuated to dryness. The residue was partitioned between methylene chloride and saturated $NaHCO_3$ solution. The organic phase was washed with water and dried (magnesium sulphate). The residue was purified by column chromatography on an ion exchange column (isolute SCX-2 column from International Sorbent Technology Limited, Henoed, Mid-Glamorgan, UK) using initially methylene chloride and then a 49:1 mixture of methanol and aqueous ammonia solution to give the title compound (0.137 g); NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.70 (m, 2H), 1.96 (m, 1H), 2.14 (s, 3H), 2.32 (s, 3H), 2.57 (d, 1H), 2.87 (m, 2H), 3.29 (d, 1H), 3.45 (m, 1H), 3.56 (s, 1H), 4.50 (d, 1H), 7.13 (d, 1H), 7.26 (m, 1H), 7.52 (d, 1H), 7.61 (d, 1H), 7.81 (m, 1H), 7.90 (m, 1H), 7.99 (s, 1H), 8.43 (d, 1H); Mass Spectrum: $M+H^+$ 430.

Example 5

***N*-cyclopropyl-4-methyl-3-[6-(4-methylpiperazin-1-yl)-4-oxoquinazolin-3(4H)-yl]benzamide**

To a stirred slurry of 4-methyl-3-[6-(4-methylpiperazin-1-yl)-4-oxoquinazolin-3(4H)-yl]benzoic acid (0.2 g) and DMF (0.05 ml) in methylene chloride (4 ml) at 35°C was added thionyl chloride (0.019 ml). The resultant yellow solution was stirred at 35°C for 2.5 hours. The reaction mixture was concentrated to give a yellow / orange solid. The solid was stirred in methylene chloride (4 ml) at room temperature and cyclopropylamine (0.37 ml) was added, stirred for 10 minutes and concentrated. The resultant solid was partitioned between ethyl acetate (5 ml) and a saturated $NaHCO_3$ solution (2.5 ml). The aqueous layer was separated and the organic layer washed with brine (5 ml). The organic phase concentrated to give a yellow foam and white solid. The mixture was triturated with toluene (5 mL) and filtered to remove the inorganic residues. The toluene solution was concentrated to give a yellow gum which was dissolved in methylene chloride and concentrated (3 times) to give the title compound as a yellow foam (171 mg); NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.70 (m, 2H), 2.13 (s, 3H), 2.24 (s, 3H), 2.48 (m, 4H), 2.86 (m, 1H), 3.29 (m, 4H), 7.48 (d, 1H), 7.53 (d, 1H), 7.64 (m, 2H), 7.82 (d, 1H), 7.90 (m, 1H), 8.09 (s, 1H), 8.43 (d, 1H); Mass Spectrum: $M+H^+$ 418.

The 4-methyl-3-[6-(4-methylpiperazin-1-yl)-4-oxoquinazolin-3(4*H*)-yl]benzoic acid used for the starting material was prepared as follows:-

To a stirred solution of methyl 5-bromo-2-aminobenzoate (10.0 g) and methyl 3-amino-4-methylbenzoate (7.90 g) in toluene (100 ml) at 50°C were added triethylorthoformate (8.12 ml) and glacial acetic acid (2.50 ml). The mixture was heated to reflux for 16 hours. The alcohol by-products were distilled using Dean-stark conditions and the reaction cooled room temperature. The resultant solid was collected by filtration, washed with toluene (2 x 20 ml) and dried *in vacuo* at 40°C to give the title compound as a white solid (13.1 g); NMR Spectrum: ($DMSOd_6$) 2.16 (s, 3H), 3.85 (s, 3H), 7.60 (d, 1H), 7.71 (d, 1H), 8.01 (m, 3H), 8.26 (s, 1H), 8.34 (s, 1H); Mass Spectrum: $M+H^+$ 373.

To a stirred suspension of methyl 3-(6-bromo-4-oxoquinazolin-3(4H)-yl)-4-methylbenzoate (15.0 g), Cs_2CO_3 (26.2 g), racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (1.88 g), palladium acetate (0.46 g) in anhydrous toluene (150 ml) at ambient temperature was added *N*-methyl piperazine (5.99 ml). The mixture was heated to 100°C and

stirred for 16 hours. Inorganic solids were removed via a hot filtration and the filtrate was allowed to cool to room temperature with stirring to crystallise the product. The mixture was stirred for 16 hours and the solid isolated by filtration, washed with toluene (3 x 10 ml) and dried *in vacuo* at 40°C to give the title compound as a yellow solid (8.44 g); NMR Spectrum: ($DMSOd_6$): 2.15 (s, 3H), 2.23 (s, 3H), 2.48 (m, 4H), 3.29 (m, 4H), 3.85 (s, 3H), 7.46 (m, 1H), 7.58 (m, 3H), 7.98 (m, 2H), 8.07 (s, 1H); Mass Spectrum: $M+H^+$ 393.

To a stirred suspension of methyl 4-methyl-3-[6-(4-methylpiperazin-1-yl)-4-oxoquinazolin-3(4H)-yl]benzoate (0.5 g) in methanol (5 ml) at 65°C was added 1N NaOH (1.6 ml) and was stirred at 65°C for 30 minutes. The mixture was acidified by addition of 1N HCl (1.6 ml) over 5 minutes and the reaction mixture cooled to room temperature over 1 hour and stirred for a further 30 minutes. The resultant solid was isolated by filtration, washed with water (2 mL), methanol/water (1:1, 2 mL), methanol (2 x 2 mL) and dried in vacuo at 40°C to give the title compound as an off-white solid (0.4 g); NMR Spectrum: ($DMSOd_6$) 2.14 (s, 3H), 2.78 (s, 3H), 3.25 (m, 8H), 7.57 (m, 2H), 7.68 (s, 2H), 7.91 (m, 1H), 7.98 (m, 1H), 8.12 (s, 1H); Mass Spectrum: $M+H^+$ 379.

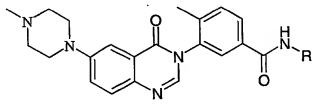
Example 6

***N*-cyclobutyl-4-methyl-3-[6-(4-methylpiperazin-1-yl)-4-oxoquinazolin-3(4*H*)-yl]benzamide**

Phosphorus oxychloride (0.08 ml) was added to a mixture of 4-methyl-3-[6-(4-methylpiperazin-1-yl)-4-oxoquinazolin-3(4*H*)-yl]benzoic acid (0.30 g), cyclobutylamine (0.09 ml) and pyridine (5 ml) and the resultant was heated to 120°C for 5 minutes in a microwave (Personal Chemistry Emrys Optimizer with 300W magnetron). The mixture was evaporated. The residue was partitioned between ethyl acetate and saturated $NaHCO_3$ solution. The organic phase was dried (magnesium sulphate) and evaporated and the residue purified by column chromatography on a silica column using initially methylene chloride and then a 9:1 mixture of methylene chloride and methanol as eluent. There was thus obtained the title compound (0.16 g); NMR Spectrum: ($DMSOd_6$) 1.68 (m, 2H), 2.05 (m, 2H), 2.14 (s, 3H), 2.20 (m, 2H), 2.24 (s, 3H), 2.48 (m, 4H), 3.29 (m, 4H), 4.42 (m, 1H), 7.49 (d, 1H), 7.53 (d, 1H), 7.65 (m, 2H), 7.87 (d, 1H), 7.92 (m, 1H), 8.10 (s, 1H), 8.60 (d, 1H); Mass Spectrum: $M+H^+$ 432.

Using an analogous procedure to that described in Example 6, 4-methyl-3-[6-(4-methylpiperazin-1-yl)-4-oxoquinazolin-3(4*H*)-yl]benzoic acid was reacted with the appropriate amine to give the compounds described in Table 2

Table 2



R	Method	Note
1-Methylcyclopropyl (AZ12225481)	Ex 5	a
Cyclopentyl	Ex 5	b
Cyclopent-3ene	Ex 5	c

Notes

a) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.61 (m, 2H), 0.74 (m, 2H), 1.37 (s, 3H), 2.13 (s, 3H), 2.24 (s, 3H), 2.48 (m, 4H), 3.28 (m, 4H), 7.50 (m, 2H), 7.64 (m, 2H), 7.82 (s, 1H), 7.89 (m, 1H), 8.08 (s, 1H), 8.65 (s, 1H); Mass Spectrum: $M+H^+$ 432.

The (1-methylcyclopropyl)amine hydrochloride used as starting material was prepared as follows :-

Diphenylphoshoryl azide (10.5 ml) was added to a stirred mixture of 1-methylcyclopropane carboxylic acid (4.88 g) and triethylamine (6.8 ml) in anhydrous *tert*-butanol (100 ml) under an argon atmosphere. The mixture was heated to 50°C and stirred for 15 minutes. The reaction mixture was then heated to 100°C and stirred for 16 hours. The reaction mixture was evaporated, dissolved in diethyl ether and washed with a saturated $NaHCO_3$ solution, water and dried (magnesium sulphate) to give the title compound as a solid (3.61 g); NMR Spectrum: ($DMSOd_6$) 0.45 (m, 2H), 0.58 (m, 2H), 1.22 (s, 3H), 1.37 (s, 9H), 7.01 (s, 1H).

tert-Butyl(1-methylcyclopropyl)carbamate (3.60 g) was dissolved in 10% HCl in methanol (20 ml) and heated to 50°C for 6 hours. The reaction mixture was evaporated *in vacuo* and diethyl ether added. The mixture was evaporated to give the title compound as a

solid (2.24 g); NMR Spectrum: ($DMSOd_6$) 0.60 (m, 2H), 0.92 (m, 2H), 1.35 (s, 3H), 8.45 (s, 3H).

b) The product gave the following data; Mass Spectrum $M+H^+$ 446.

c) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 2.14 (s, 3H), 2.24 (s, 3H), 2.32 (m, 2H), 2.48 (m, 4H), 2.68 (m, 2H), 3.28 (m, 4H), 4.56 (m, 1H), 5.73 (s, 2H), 7.48 (d, 1H), 7.53 (d, 1H), 7.64 (m, 2H), 7.89 (d, 1H), 7.94 (m, 1H), 8.10 (s, 1H), 8.50 (d, 1H); Mass Spectrum: $M+H^+$ 444.

Example 7

***N*-cyclopropyl-4-methyl-3-[4-oxo-6-(4-propyl-1,4-diazepan-1-yl)quinazolin-3(4*H*)-yl]benzamide**

1-Iodopropane (0.039 ml) was added to a stirred mixture of *N*-cyclopropyl-3-[6-(1,4-diazepan-1-yl)-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide (0.150 g) and potassium carbonate (0.199 g) in DMA (0.50 ml). The mixture was stirred at room temperature for 16 hours. The reaction mixture was poured into water (20 ml), the resulting solid was filtered and dried (magnesium sulphate) under vacuum at 40°C. There was thus obtained the title compound (0.098 g); NMR Spectrum: ($DMSOd_6$) 0.54 (m, 2H), 0.68 (m, 2H), 0.80 (t, 3H), 1.39 (m, 2H), 1.87 (m, 2H), 2.11 (s, 3H), 2.36 (t, 2H), 2.49 (m, 2H), 2.72 (m, 2H), 2.84 (m, 1H), 3.56 (m, 4H), 7.23 (d, 1H), 7.36 (d, 1H), 7.50 (d, 1H), 7.58 (d, 1H), 7.79 (s, 1H), 7.87 (d, 1H), 7.95 (s, 1H), 8.41 (d, 1H); Mass Spectrum: $M+H^+$ 460.

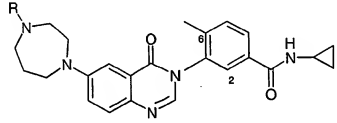
The *N*-cyclopropyl-3-[6-(1,4-diazepan-1-yl)-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide used as starting material was prepared as follows:-

tert-butyl 4-(3-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4-oxo-3,4-dihydroquinazolin-6-yl)-1,4-diazepane-1-carboxylate (1.04 g) was dissolved in 10% HCl in methanol (20 ml) and heated to 40°C for 90 minutes. The solvent was evaporated *in vacuo* and the residue basified with a saturated $NaHCO_3$ solution. The pH of the solution was adjusted to pH 4-5 with 1N citric acid and the solution poured onto an ion exchange column (isolute SCX-2 column from International Sorbent Technology Limited, Henoed, Mid-Glamorgan, UK). The column was washed with water (2 x 50 ml), methanol (2 x 50 ml) and the product eluted with 2N ammonia in methanol. The fractions containing product were evaporated *in vacuo* to give the title compound (0.75 g); NMR Spectrum: ($DMSOd_6$) 0.54 (m, 2H), 0.68 (m, 2H), 1.79 (m, 2H), 2.12 (s, 3H), 2.63 (m, 2H), 2.86 (m, 3H), 3.55 (t, 2H), 3.63

(t, 2H), 7.23 (m, 1H), 7.36 (m, 1H), 7.50 (d, 1H), 7.58 (d, 1H), 7.79 (d, 1H), 7.88 (m, 1H), 7.95 (s, 1H); Mass Spectrum: $M+H^+$ 418.

Using an analogous procedure to that described in Example 7, *N*-cyclopropyl-3-[6-(1,4-diazepan-1-yl)-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide was reacted with the appropriate alkyl halide to give the compounds described in Table 3.

Table 3



R	Method	Note
Ethyl (AZ12188893)	Ex 6	a
2-Amino-2-oxoethyl (AZ12188901)	Ex 6	b
2-Methoxyethyl (AZ12188894)	Ex 6	c
Cyclopropylmethyl (AZ12188892)	Ex 6	d

Notes

a) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.52 (m, 2H), 0.66 (m, 2H), 0.96 (t, 3H), 1.87 (m, 2H), 2.12 (s, 3H), 2.46 (m, 2H), 2.71 (m, 2H), 2.84 (m, 1H), 3.54 (m, 4H), 7.23 (s, 1H), 7.36 (m, 1H), 7.49 (m, 1H), 7.58 (m, 1H), 7.78 (s, 1H), 7.87 (d, 1H), 7.96 (s, 1H), 8.40 (d, 1H); Mass Spectrum: $M+H^+$ 446.

b) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.54 (m, 2H), 0.67 (m, 2H), 1.90 (m, 2H), 2.10 (s, 3H), 2.58 (m, 2H), 2.81 (m, 3H), 2.99 (s, 2H), 3.61 (m, 4H), 7.05 (s, 1H), 7.12 (s, 1H), 7.23 (s, 1H), 7.37 (m, 1H), 7.50 (d, 1H), 7.58 (d, 1H), 7.79 (s, 1H), 7.87 (d, 1H), 7.96 (s, 1H), 8.41 (d, 1H); Mass Spectrum: $M+H^+$ 475.

c) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.54 (m, 2H), 0.67 (m, 2H), 1.83 (m, 2H), 2.15 (s, 3H), 2.59 (m, 4H), 2.84 (m, 3H), 3.30 (s, 3H), 3.38 (m, 2H), 3.58 (m, 4H), 7.24 (s, 1H), 7.36 (d, 1H), 7.50 (d, 1H), 7.58 (d, 1H), 7.79 (s, 1H), 7.87 (d, 1H), 7.96 (s, 1H), 8.40 (d, 1H); Mass Spectrum: $M+H^+$ 476

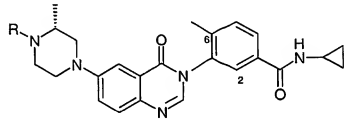
d) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.02 (m, 2H), 0.40 (m, 2H), 0.52 (m, 2H), 0.66 (m, 2H), 1.88 (m, 2H), 2.10 (s, 3H), 2.30 (m, 2H), 2.58 (m, 2H),

2.81 (m, 3H), 3.52 (m, 2H), 3.59 (m, 2H), 7.21 (m, 1H), 7.35 (m, 1H), 7.48 (d, 1H), 7.57 (d, 1H), 7.77 (s, 1H), 7.86 (d, 1H), 7.95 (s, 1H), 8.39 (m, 1H); Mass Spectrum: $M+H^+$ 472.

Example 8

Using an analogous procedure to that described in Example 7, the *N*-cyclopropyl-4-methyl-3-[6-[(3R)-3-methylpiperazin-1-yl]-4-oxoquinazolin-3(4H)-yl]benzamide starting material was reacted the appropriate alkylating reagent to give the compounds described in Table 4.

Table 4



R	Method	Note
Ethyl (AZ12263563)	Ex 6	a
Isopropyl (AZ12264041)	Ex 6	b
Cyclopropylmethyl (AZ12264627)	Ex 6	c

a) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.57 (m, 2H), 0.70 (m, 2H), 1.00 (t, 3H), 1.08 (d, 3H), 2.14 (s, 3H), 2.36 (m, 2H), 2.62 (m, 1H), 2.87 (m, 3H), 3.28 (m, 2H), 3.60 (m, 2H), 7.47 (s, 1H), 7.53 (d, 1H), 7.64 (s, 2H), 7.82 (s, 1H), 7.90 (m, 1H), 8.08 (s, 1H), 8.43 (m, 1H); Mass spectrum: $M+H^+$ 446.

b) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.70 (m, 2H), 0.88 (d, 3H), 1.09 (d, 6H), 2.14 (s, 3H), 2.40 (m, 1H), 2.58 (m, 1H), 2.70 (m, 1H), 2.85 (m, 3H), 3.22 (m, 1H), 3.65 (m, 2H), 7.46 (s, 1H), 7.53 (d, 1H), 7.63 (m, 2H), 7.82 (d, 1H), 7.90 (m, 1H), 8.08 (s, 1H), 8.43 (d, 1H); Mass Spectrum: $M+H^+$ 460.

c) The product gave the following data; NMR Spectrum: ($DMSOd_6$) -0.01 (m, 2H), 0.36 (m, 2H), 0.45 (m, 2H), 0.58 (m, 2H), 0.75 (m, 1H), 0.96 (d, 3H), 2.02 (s, 3H), 2.06 (m, 1H), 2.33 (m, 1H), 2.49 (m, 3H), 2.75 (m, 1H), 2.83 (m, 1H), 3.00 (m, 1H), 3.51 (m, 2H), 7.35 (s, 1H), 7.41 (d, 1H), 7.53 (s, 2H), 7.71 (d, 1H), 7.79 (m, 1H), 7.97 (s, 1H), 8.31 (d, 1H); Mass Spectrum: $M+H^+$ 472.

Example 9

***N*-cyclopropyl-4-methyl-3-[4-oxo-6-(4-propylpiperazin-1-yl)quinazolin-3(4*H*)-yl]benzamide**

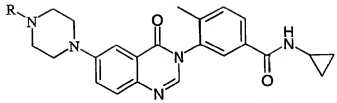
1-Iodopropane (0.039 ml) was added to a stirred mixture of *N*-cyclopropyl-4-methyl-3-(4-oxo-6-piperazin-1-ylquinazolin-3(4*H*)-yl)benzamide (0.145 g) and potassium carbonate (0.199 g) in DMA (0.50 ml). The mixture was stirred at room temperature for 16 hours. The reaction mixture was poured into water (20 ml), the resulting solid was filtered and dried (magnesium sulphate) under vacuum at 40°C. There was thus obtained the title compound (0.109 g); NMR Spectrum: ($DMSOd_6$) 0.54 (m, 2H), 0.68 (m, 2H), 0.87 (t, 3H), 1.48 (m, 2H), 2.12 (s, 3H), 2.28 (t, 2H), 2.50 (m, 4H), 2.84 (m, 1H), 3.27 (m, 4H), 7.45 (s, 1H), 7.50 (d, 1H), 7.62 (s, 2H), 7.80 (s, 1H), 7.87 (d, 1H), 8.06 (s, 1H), 8.41 (d, 1H); Mass Spectrum: $M+H^+$ 446.

The *N*-cyclopropyl-4-methyl-3-(4-oxo-6-piperazin-1-ylquinazolin-3(4*H*)-yl)benzamide used as starting material was prepared as follows :

tert-Butyl 4-(3-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4-oxo-3,4-dihydroquinazolin-6-yl)piperazine-1-carboxylate (0.72 g) was dissolved in 10% HCl in methanol (20 ml) and heated to 40°C for 90 minutes. The solvent was evaporated *in vacuo* and the residue basified with saturated $NaHCO_3$ solution. The pH of the solution was adjusted to pH 4-5 with 1N Citric acid and the solution poured onto an ion exchange column (isolute SCX-2 column from International Sorbent Technology Limited, Henoed, Mid-Glamorgan, UK). The column was washed water (2 x 50 ml), methanol (2 x 50 ml) and the product eluted with 2N ammonia in methanol. The fractions containing product were evaporated *in vacuo* to give the title compound (0.51 g). NMR Spectrum: ($DMSOd_6$) 0.55 (m, 2H), 0.67 (m, 2H), 2.12 (s, 3H), 2.85 (m, 5H), 3.20 (m, 4H), 7.51 (m, 2H), 7.61 (m, 2H), 7.81 (s, 1H), 7.89 (m, 1H), 8.07 (s, 1H), 8.42 (m, 1H); Mass Spectrum $M+H^+$ 404.

Using an analogous procedure to that described in Example 7, the *N*-cyclopropyl-4-methyl-3-(4-oxo-6-piperazin-1-ylquinazolin-3(4*H*)-yl)benzamide was reacted with the appropriate alkyl halide to give the compounds described in Table 5.

Table 5



R	Method	Note
Cyclopropylmethyl (AZ12193780)	Ex 9	a
2-Methoxyethyl (AZ12193781)	Ex 9	b
Cyanomethyl (AZ12226767)	Ex 9	c
Prop-2-yn-1-yl (AZ12226769)	Ex 9	d
2-Fluoroethyl (AZ12257430)	Ex 9	e
2,2-Difluoroethyl (AZ12257434)	Ex 9	f
2-(Tetrahydro-2*H*-pyran-2-yloxy)ethyl (AZ12257438)	Ex 9	g
2,2,2-Trifluoro-1-methylethyl (AZ12273151)	Ex 9	h
Cyclobutyl (AZ12228643)	Ex 9	i
Acetyl (AZ12228233)		j
(5-Methylisoxazol-3-yl)methyl (AZ12251835)	Ex 9	k
1,3-Thiazol-4-ylmethyl (AZ12251834)	Ex 9	l

Notes

a) The product gave the following data; Mass Spectrum: $M+H^+$ 458.

b) The product gave the following data; Mass Spectrum: $M+H^+$ 476.

c) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.55 (m, 2H), 0.68 (m, 2H), 2.11 (s, 3H), 2.64 (m, 4H), 2.84 (m, 1H), 3.32 (m, 4H), 3.80 (s, 2H), 7.50 (m, 2H), 7.63 (s, 2H), 7.80 (s, 1H), 7.88 (d, 1H), 8.08 (s, 1H), 8.41 (d, 1H); Mass Spectrum: $M+Na^+$ 465.

d) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.53 (m, 2H), 0.68 (m, 2H), 2.12 (s, 3H), 2.61 (m, 4H), 2.85 (m, 1H), 3.15 (m, 1H), 3.30 (m, 6H), 7.49 (m, 2H), 7.63 (s, 2H), 7.80 (s, 1H), 7.88 (d, 1H), 8.07 (s, 1H), 8.41 (d, 1H); Mass Spectrum: $M+H^+$ 442.

e) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.53 (m, 2H), 0.67 (m, 2H), 2.13 (s, 3H), 2.62 (m, 4H), 2.79 (m, 3H), 3.28 (m, 4H), 4.48 (m, 1H), 4.64 (m, 1H),

7.49 (m, 2H), 7.63 (s, 2H), 7.80 (s, 1H), 7.88 (m, 1H), 8.07 (s, 1H), 8.42 (d, 1H); Mass Spectrum: M+H$^+$ 450.

f) The product gave the following data; NMR Spectrum: (DMSOd_6) 0.53 (m, 2H), 0.68 (m, 2H), 2.12 (s, 3H), 2.70 (m, 4H), 2.83 (m, 3H), 3.28 (m, 4H), 6.16 (m, 1H), 7.49 (m, 2H), 7.62 (s, 2H), 7.79 (s, 1H), 7.88 (d, 1H), 8.07 (s, 1H), 8.42 (d, 1H); Mass Spectrum: M+H$^+$ 468.

g) The product gave the following data; NMR Spectrum: (DMSOd_6) 0.54 (m, 2H), 0.68 (m, 2H), 1.56 (m, 6H), 2.10 (s, 3H), 2.48 (m, 2H), 2.61 (m, 4H), 2.84 (m, 1H), 3.27 (m, 4H), 3.46 (m, 2H), 3.75 (m, 2H), 4.56 (m, 1H), 7.45 (s, 1H), 7.50 (d, 1H), 7.62 (s, 2H), 7.80 (s, 1H), 7.88 (d, 1H), 8.08 (s, 1H), 8.41 (d, 1H); Mass Spectrum: M+H$^+$ 532.

h) The product gave the following data; NMR Spectrum: (DMSOd_6) 0.55 (m, 2H), 0.67 (m, 2H), 2.11 (s, 3H), 2.53 (m, 7H), 2.84 (m, 1H), 3.27 (m, 4H), 3.54 (m, 1H), 7.49 (m, 2H), 7.63 (s, 2H), 7.80 (s, 1H), 7.88 (d, 1H), 8.08 (s, 1H), 8.41 (m, 1H); Mass Spectrum: M+H$^+$ 500.

i) The product gave the following data; NMR Spectrum: (DMSOd_6) 0.01 (m, 2H), 0.42 (m, 4H), 0.58 (m, 2H), 0.74 (m, 2H), 2.03 (s, 3H), 2.15 (d, 2H), 2.32 (m, 1H), 2.50 (m, 2H), 2.74 (m, 1H), 3.18 (m, 4H), 7.38 (s, 1H), 7.42 (d, 1H), 7.54 (s, 2H), 7.72 (s, 1H), 7.80 (d, 1H), 7.98 (s, 1H), 8.33 (d, 1H); Mass Spectrum: M+H$^+$ 458.

j) *N*-Cyclopropyl-4-methyl-3-(4-oxo-6-piperazin-1-ylquinazolin-3(4*H*)-yl)benzamide was dissolved in methylene chloride (2 ml) and treated with *N*,*N*-diisopropylethylamine (0.13 ml) and acetyl chloride (0.06 ml). After stirring for 2hrs the solid was collected by filtration, washed methylene chloride (2x) to give the title compound; NMR Spectrum: (DMSOd_6) 0.62 (m, 4H), 2.13 (s, 3H), 2.13 (s, 3H), 2.84 (m, 1H), 3.31 (m, 4H), 3.63 (m, 4H), 7.53 (m, 2H), 7.70 (m, 2H), 7.90 (m, 2H), 8.33 (s, 1H), 8.49 (d, 1H); Mass Spectrum: M+H$^+$ 446.

k) The product gave the following data; NMR Spectrum: (DMSOd_6) 0.61 (m, 4H), 2.11 (s, 3H), 2.38 (s, 3H), 2.57 (m, 4H), 2.84 (m, 1H), 3.26 (m, 4H), 3.55 (s, 2H), 6.20 (s, 1H), 7.49 (m, 2H), 7.61 (m, 2H), 7.80 (m, 1H), 7.88 (m, 1H), 8.07 (m, 1H), 8.42 (d, 1H); Mass Spectrum: M+H$^+$ 499.

l) The product gave the following data; NMR Spectrum: (DMSOd_6) 0.61 (m, 4H), 2.10 (s, 3H), 2.62 (m, 4H), 2.85 (m, 1H), 3.28 (m, 4H), 3.73 (s, 2H), 7.50 (m, 3H), 7.61 (m, 2H), 7.80 (d, 1H), 7.88 (m, 1H), 8.08 (d, 1H), 8.41 (d, 1H), 9.05 (d, 1H); Mass Spectrum: M+H$^+$ 501.

Example 10

***N*-cyclopropyl-4-methyl-3-[6-(4-isopropylpiperazin-1-yl)-4-oxoquinazolin-3(4*H*)-yl]benzamide (AZ12239931)**

Phosphorus oxychloride (0.11 ml) was added to a mixture of 4-methyl-3-[6-(4-isopropylpiperazin-1-yl)-4-oxoquinazolin-3(4*H*)-yl]benzoic acid (0.30 g), 1-methylcyclopropylamine hydrochloride (0.13 g) and pyridine (5 ml) and the resultant was heated to 120°C for 5 minutes in a microwave (Personal Chemistry Emrys Optimizer with 300W magnetron). The mixture was evaporated. The residue was partitioned between ethyl acetate and saturated $NaHCO_3$ solution. The organic phase was dried (magnesium sulphate) and evaporated and the residue purified by column chromatography on a silica column using initially methylene chloride and then a 9:1 mixture of methylene chloride and methanol as eluent. There was thus obtained the title compound (0.13 g); NMR Spectrum: ($CDCl_3$) 0.76 (m, 4H), 1.09 (d, 6H), 2.20 (s, 3H), 2.20 (s, 3H), 2.72 (m, 5H), 3.35 (m, 4H), 6.61 (s, 1H), 7.43 (m, 2H), 7.66 (m, 3H), 7.78 (m, 2H); Mass Spectrum: $M+H^+$ 460.

The 4-methyl-3-[6-(4-isopropylpiperazin-1-yl)-4-oxoquinazolin-3(4*H*)-yl]benzoic acid used for the starting material was prepared as follows:-

Using an analogous procedure to that described paragraph (B) in the portion of Example 1 which is concerned with the preparation of starting material *N*-isopropylpiperazine was reacted with 5-fluoro-2-nitrobenzoic acid to give methyl 3-[(5-fluoro-2-nitrobenzoyl)amino]-4-methylbenzoate to give methyl 4-methyl-3-{[5-(4-isopropylpiperazin-1-yl)-2-nitrobenzoyl]amino}benzoate; NMR Spectrum: ($DMSOd_6$) 0.99 (d, 6H), 2.34 (s, 3H), 2.55 (m, 4H), 2.71 (m, 1H), 3.50 (m, 4H), 3.85 (s, 3H), 7.07 (m, 2H), 7.39 (d, 1H), 7.71 (m, 1H), 8.06 (d, 1H), 8.20 (m, 1H), 9.96 (s, 1H); Mass Spectrum: $M+H^+$ 441.

Using an analogous procedure to that described paragraph (C) in the portion of Example 1 which is concerned with the preparation of starting materials, methyl 4-methyl-3-{[5-(4-isopropylpiperazin-1-yl)-2-nitrobenzoyl]amino}benzoate was reduced to methyl 3-{[2-amino-5-(4-isopropylpiperazin-1-yl)benzoyl]amino}-4-methylbenzoate; Mass Spectrum: $M+H^+$ 411.

Using an analogous procedure to that described in Example 1, methyl 3-{[2-amino-5-(4-isopropylpiperazin-1-yl)benzoyl]amino}-4-methylbenzoate was reacted with triethylorthoformate to give methyl 4-methyl-3-[6-(4-isopropylpiperazin-1-yl)-4-oxoquinazolin-3(4*H*)-yl]benzoate; NMR Spectrum: ($DMSOd_6$) 1.00 (d, 6H), 2.15 (s, 3H),

2.59 (m , 4H), 2.68 (m , 1H), 3.24 (m , 4H), 3.85 (s, 3H), 7.45 (d, 1H), 7.60 (m , 3H), 7.95 (m , 1H), 8.00 (m , 1H), 8.05 (d, 1H); Mass Spectrum: $M+H^+$ 421.

Methyl 4-methyl-3-[6-(4-isopropylpiperazin-1-yl)-4-oxoquinazolin-3(4*H*)-yl]benzoate 7.56 g) was dissolved in a mixture of methanol (135 ml) and water (45 ml). 2N NaOH (36 ml) added and stirred at room temperature for 1 hour. The pH was adjusted to 2-3 using 2N HCl and the solvent evaporated *in vacuo*. The oil was triturated with a mixture of ethyl acetate (100 ml) and *iso*-hexane (100 ml) and the solid collected by filtration and dried under vacuum at 40°C for 16 hours to give the title compound (9.9 g); NMR Spectrum: ($DMSOd_6$) 1.33 (d, 6H), 2.14 (s, 3H), 3.15 (m, 2H), 3.46 (m, 5H), 3.98 (m, 2H), 7.55 (m, 2H), 7.68 (m, 2H), 7.89 (m, 1H), 7.98 (m, 1H), 8.18 (t, 1H), 11.56 (s, 1H); Mass Spectrum: $M+H^+$ 407.

Using an analogous procedure to that described paragraph (A) in the portion of Example 6 which is concerned with the preparation of starting material, cyclobutylamine was reacted with 4-methyl-3-[6-(4-isopropylpiperazin-1-yl)-4-oxoquinazolin-3(4*H*)-yl]benzoic acid to give *N*-cyclobutyl-4-methyl-3-[6-(4-isopropylpiperazin-1-yl)-4-oxoquinazolin-3(4*H*)-yl]benzamide (AZ12239932); NMR Spectrum: ($CDCl_3$) 1.11 (d, 6H), 1.75 (m, 2H), 1.93 (m, 2H), 2.23 (s, 3H), 2.41 (m, 2H), 2.75 (m, 5H), 3.38 (m, 4H), 4.57 (m, 1H), 6.30 (d, 1H), 7.26 (s, 1H), 7.44 (m, 2H), 7.66 (m, 2H), 7.79 (m, 2H); Mass Spectrum: $M+H^+$ 460.

Example 11

***N*-cyclopropyl-4-methyl-3-[7-(4-methylpiperazin-1-yl)-4-oxoquinazolin-3(4*H*)-yl]benzamide (AZ12240198)**

Triethylorthoformate (0.18 ml) was added to a stirred mixture of 2-amino-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4-(4-methylpiperazin-1-yl)benzamide (0.152 g) and glacial acetic acid (0.011 ml) in ethanol (30 ml). The mixture was heated to 90°C and stirred for 16 hours. To the mixture was added 1N HCl (1 ml) and heated to 90°C for 2 hours. The reaction mixture was made basic with sodium bicarbonate and evaporated, dissolved in ethyl acetate and washed with water. The organic phase was dried (magnesium sulphate) and evaporated to give the title compound (0.098 g); NMR Spectrum: ($DMSOd_6$) 0.57 (m, 2H), 0.70 (m, 2H), 2.13 (s, 3H), 2.31 (s, 3H), 2.56 (m, 4H), 2.86 (m, 1H), 3.44 (m, 4H), 7.05 (d, 1H), 7.27 (m, 1H), 7.51 (d, 1H), 7.80 (d, 1H), 7.89 (m, 1H), 7.99 (d, 1H), 8.16 (s, 1H), 8.43 (d, 1H); Mass Spectrum: $M+H^+$ 418.

The 2-amino-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4-(4-methylpiperazin-1-yl)benzamide used as starting material was prepared as follows :-

N,*N*-Diisopropylethylamine (0.30 ml) was added to a stirred mixture of *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4-fluoro-2-nitrobenzamide (0.30 g) and *N*-methylpiperazine (0.28 ml) in DMSO (0.5 ml). The mixture was heated to 90°C and stirred for 16 hours. The reaction mixture was poured into water (100 ml), the resulting solid was filtered, washed with water, diethyl ether and redissolved in methylene chloride. The organic phase was dried (diatomaceous earth column) and evaporated to give the title compound as a solid (0.23 g); NMR Spectrum: ($DMSOd_6$) 0.58 (m, 2H), 0.69 (m, 2H), 2.24 (s, 3H), 2.29 (s, 3H), 2.46 (m, 4H), 2.85 (m, 1H), 3.36 (m, 4H), 7.30 (m, 2H), 7.45 (d, 1H), 7.61 (m, 1H), 7.67 (d, 1H), 7.83 (s, 1H), 8.39 (d, 1H), 10.03 (s, 1H); Mass Spectrum: $M+H^+$ 438.

A suspension of *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4-(4-methylpiperazin-1-yl)-2-nitrobenzamide (0.23 g) and 10% palladium on carbon (0.04 g) in ethanol (30 ml) was agitated under a hydrogen atmosphere for 16 hours. The reaction mixture was filtered through diatomaceous earth (Celite®) and the filtrate evaporated to dryness to give the title compound as a glass (0.16 g); NMR Spectrum: ($DMSOd_6$) 0.57 (m, 2H), 0.68 (m, 2H), 2.22 (s, 3H), 2.24 (s, 3H), 2.43 (m, 4H), 2.85 (m, 1H), 3.19 (m, 4H), 6.18 (s, 1H), 6.25 (m, 1H), 6.44 (s, 2H), 7.30 (d, 1H), 7.59 (m, 1H), 7.64 (d, 1H), 7.76 (s, 1H), 8.35 (d, 1H), 9.37 (s, 1H); Mass Spectrum: $M+H^+$ 408.

Example 12

***N*-cyclopropyl-4-methyl-3-[8-(4-methylpiperazin-1-yl)-4-oxoquinazoline-3(4*H*)-yl]benzamide (AZ12302462)**

Using an analogous procedure to that described in Example 1, 2-amino-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-3-(4-methylpiperazine-1-yl)benzamide was reacted with trimethylorthoformate. There was thus obtained the title compound; NMR Spectrum: ($DMSOd_6$) 0.55 (m, 2H), 0.67 (m, 2H), 2.13 (s, 3H), 2.24 (s, 3H), 2.50 (m, 4H), 2.84 (m, 1H), 3.31 (m, 4H), 7.33 (d, 1H), 7.48 (m, 2H), 7.78 (m, 2H), 7.88 (d, 1H), 8.25 (s, 1H), 8.41 (d, 1H); Mass Spectrum: $M+H^+$ 418

The 2-amino-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-3-(4-methylpiperazine-1-yl)benzamide used as starting material was prepared as follows :-

A) 3-amino-*N*-cyclopropyl-4-methylbenzamide (2.50 g) was added to a stirred solution of 3-chloro-2-nitrobenzoic acid (3.46 g), pyridine (2.77 ml) and HATU (6.46 g) in DMF (25 ml). The mixture was stirred at room temperature for 16 hours. The reaction mixture was poured into a saturated $NaHCO_3$ solution (1000 ml) and the resulting solid was filtered and dried

under vacuum at 40°C. There was thus obtained 3-chloro-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-2-nitrobenzamide (4.44 g); NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.67 (m, 2H), 2.25 (s, 3H), 2.83 (m, 1H), 7.32 (d, 1H), 7.62 (d, 1H), 7.80 (m, 2H), 7.96 (m, 2H), 8.39 (s, 1H), 10.46 (s, 1H); Mass Spectrum: $M+Na^+$ 396.

B) N-Methylpiperazine (2.40 ml) was added to a stirred solution of 3-chloro-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-2-nitrobenzamide (1.0 g) in DMSO (2.0 ml). The mixture was heated to 80°C and stirred for 40 hours. The cooled mixture was poured into a saturated $NaHCO_3$ solution (100 ml) and the resulting solid was filtered and dried under vacuum at 40°C. There was thus obtained *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-3-(4-methyl-piperazin-1-yl)-2-nitrobenzamide (0.84 g); NMR Spectrum: ($DMSOd_6$) 0.58 (m, 2H), 0.66 (m, 2H), 2.20 (s, 3H), 2.25 (s, 3H), 2.38 (m, 4H), 2.83 (m, 1H), 2.94 (m, 4H), 7.31 (d, 1H), 7.65 (m, 4H), 7.77 (s, 1H), 8.40 (s, 1H), 10.27 (s, 1H); Mass Spectrum: $M+H^+$ 438.

C) 10% Palladium-on-carbon (0.80 g) was added to a stirred suspension of *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-3-(4-methyl-piperazin-1-yl)-2-nitrobenzamide (0.84 g) in methanol (20 ml) and the mixture was stirred under an atmosphere of hydrogen gas at a pressure of 10 bar. After cessation of hydrogen uptake, the catalyst was removed by filtration through diatomaceous earth (Celite®). The filtrate was concentrated under reduced pressure, which provided the crude 2-amino- *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-3-(4-piperazin-1-yl)benzamide (0.689 g) which was used without further purification; NMR Spectrum: ($DMSOd_6$) 0.54 (m, 2H), 0.66 (m, 2H), 2.23 (s, 3H), 2.24 (s, 3H), 2.83 (m, 5H), 3.30 (m, 4H), 6.08 (s, 2H), 6.62 (t, 1H), 7.11 (d, 1H), 7.31 (d, 1H), 7.51 (d, 1H), 7.61 (d, 1H), 7.77 (s, 1H), 8.35 (s, 1H), 9.71 (s, 1H); Mass Spectrum: $M+H^+$ 408.

Example 13

***N*-cyclopropyl-4-methyl-3-(6-morpholin-4-yl-4-oxoquinazoline-3(4*H*)-yl)benzamide (AZ12203363)**

Triethylorthoformate (0.969 ml) was added to a stirred mixture of 2-amino-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-morpholin-4-ylbenzamide (0.67 g) and glacial acetic acid (0.05 ml) in ethanol (5 ml). The mixture was heated to 80°C and stirred for 16 hours. The reaction mixture was evaporated, dissolved in methylene chloride and washed

with a saturated $NaHCO_3$ solution. The organic phase was evaporated and the residue was purified by column chromatography on an ion exchange column (isolute SCX column from International Sorbent Technology Limited, Henoed, Mid-Glamorgan, UK) using initially methanol and then a 99:1 mixture of methanol and aqueous ammonia solution to give the title compound (0.172 g); NMR Spectrum: ($DMSOd_6$) 0.53 (m, 2H), 0.66 (m, 2H), 2.11 (s, 3H), 2.83 (m, 1H), 3.22 (m, 4H), 3.75 (m, 4H), 7.48 (m, 2H), 7.64 (m, 2H), 7.80 (s, 1H), 7.87 (m, 1H), 8.09 (s, 1H), 8.43 (m, 1H); Mass Spectrum: $M+H^+$ 405.

The 2-amino-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-morpholin-4-ylbenzamide used as starting material was prepared as follows :-

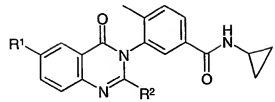
A) Morpholine (0.21 ml) was added to a stirred solution of *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-fluoro-2-nitrobenzamide (0.71g) in DMSO (1.0 ml). The mixture was stirred at room temperature for 18 hours. The mixture was poured into a saturated $NaHCO_3$ solution (100 ml) and the resultant solid was filtered and dried under vacuum at 40°C. There was thus obtained *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-morpholin-4-yl-2-nitrobenzamide (0.722 g); NMR Spectrum: ($DMSOd_6$) 0.57 (m, 2H), 0.68 (m, 2H), 2.29 (s, 3H), 2.83 (m, 1H), 3.45 (m, 4H), 3.74 (m, 4H), 7.07 (m, 2H), 7.28 (m, 1H), 7.56 (m, 1H), 7.95 (s, 1H), 8.06 (d, 1H), 8.36 (s, 1H), 9.92 (s, 1H); Mass Spectrum: $M+Na^+$ 447.

B) 10% Palladium-on-carbon (0.050 g) was added to a stirred suspension of *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-morpholin-4-yl-2-nitrobenzamide (0.722 g) in ethanol (10 ml) and the mixture was stirred under an atmosphere of hydrogen gas at a pressure of 10 bar. After cessation of hydrogen uptake, the catalyst was removed by filtration through diatomaceous earth (Celite®). The filtrate was concentrated under reduced pressure, which provided the crude 2-amino-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-morpholin-4-ylbenzamide which was used without further purification; Mass Spectrum: $M+H^+$ 395.

Example 14

Using an analogous procedure to that described in Example 13, the appropriate starting material was reacted with triethylorthoformate or triethylorthoacetate to give the compounds described in Table 6

Table 6



R^1	R^2	Method	Note
6-thiomorpholin-4-yl (AZ12203364)	H	Ex 13	a
6-(4-hydroxypiperidin-1-yl) (AZ12203366)	H	Ex 13	b
6-(3-hydroxyazetidin-1-yl) (AZ12203367)	H	Ex 13	c
6-[(3R,5S)-3,5-dimethylpiperazin-1-yl] (AZ12219137)	H	Ex 13	d
6-[(3R,5S)-3,5-dimethylpiperazin-1-yl] (AZ12193783)	Me	Ex 13	e
6-piperidin-1-yl (AZ12219143)	H	Ex 13	f
6-(4-methylpiperadin-1-yl) (AZ12219142)	H	Ex 13	g
6-[2-(Dimethylamino)ethyl]thio (AZ12285025)	H	Ex 13	h
6-(3-hydroxy-2,2-dimethylpropyl)amino (AZ12182727)	H	Ex 13	i
6-(4-methyl-1,4-diazepan-1-yl) (AZ12188891)	Me	Ex 13	j

a) *N*-cyclopropyl-4-methyl-3-(4-oxo-6-thiomorphin-4-ylquinazoline-3(4*H*)-yl)benzamide gave the following data; NMR Spectrum: ($DMSOd_6$) 0.53 (m, 2H), 0.68 (m, 2H), 2.11 (s, 3H), 2.69 (m, 4H), 2.84 (m, 1H), 3.67 (m, 4H), 7.44 (m, 1H), 7.50 (d, 1H), 7.61 (m, 2H), 7.79 (s, 1H), 7.88 (d, 1H), 8.07 (s, 1H), 8.44 (d, 1H); Mass Spectrum: $M+H^+$ 421.

The 2-amino-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-thiomorpholin-4-ylbenzamide used for the starting material was prepared as follows:-

Using an analogous procedure to that described paragraph (A) in the portion of Example 13 which is concerned with the preparation of starting materials thiomorpholine was reacted with *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-fluoro-2-nitrobenzamide to give *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-2-nitro-5-thiomorpholin-4-ylbenzamide; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.67 (m, 2H), 2.30 (s, 3H), 2.67 (m, 4H), 2.82 (m, 1H), 3.91 (m, 4H), 7.06 (m, 2H), 7.27 (d, 1H), 7.55 (d, 1H), 7.97 (s, 1H), 8.04 (d, 1H), 8.37 (s, 1H), 9.90 (s, 1H); Mass Spectrum: $M+Na^+$ 463.

Using an analogous procedure to that described paragraph (B) in the portion of Example 13 which is concerned with the preparation of starting materials, *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-2-nitro-5-thiomorpholin-4-ylbenzamide was reduced to give the required starting material; Mass Spectrum: $M+H^+$ 411.

b) *N*-cyclopropyl-3-[6-(4-hydroxypiperidin-1-yl)-4-oxoquinazoline-3(4*H*)-yl]-4-methylbenzamide gave the following data; NMR Spectrum: ($DMSOd_6$) 0.53 (m, 2H), 0.68 (m, 2H), 1.48 (m, 2H), 1.83 (m, 2H), 2.11 (s, 3H), 2.83 (m, 1H), 2.99 (t, 2H), 3.65 (m, 3H), 4.71 (d, 1H), 7.45 (s, 1H), 7.50 (d, 1H), 7.60 (s, 2H), 7.80 (s, 1H), 7.87 (d, 1H), 8.06 (s, 1H), 8.42 (m, 1H); Mass Spectrum $M+H^+$ 419.

The 2-amino-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-(4-hydroxypiperidin-1-yl)benzamide used for the starting material was prepared as follows:-

Using an analogous procedure to that described paragraph (A) in the portion of Example 13 which is concerned with the preparation of starting materials 4-hydroxypiperidine was reacted with *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-fluoro-2-nitrobenzamide to give *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-(4-hydroxypiperidin-1-yl)-2-nitrobenzamide; NMR Spectrum: ($DMSOd_6$) 0.55 (m, 2H), 0.68 (m, 2H), 1.43 (m, 2H), 1.82 (m, 2H), 2.30 (s, 3H), 2.84 (m, 1H), 3.25 (m, 2H), 3.82 (m, 3H), 4.76 (d, 1H), 7.04 (m, 2H), 7.28 (d, 1H), 7.56 (d, 1H), 7.96 (s, 1H), 8.02 (d, 1H), 8.36 (s, 1H), 9.90 (s, 1H); Mass Spectrum: $M+Na^+$ 461.

Using an analogous procedure to that described paragraph (B) in the portion of Example 13 which is concerned with the preparation of starting materials, *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-(4-hydroxypiperidin-1-yl)-2-nitrobenzamide was reduced to give the required starting material; Mass Spectrum: $M+H^+$ 409.

c) *N*-cyclopropyl-3-[6-(3-hydroxyazetidin-1-yl)-4-oxoquinazoline-3(4*H*)-yl]-4-methylbenzamide gave the following data; NMR Spectrum: ($DMSOd_6$) 0.53 (m, 2H), 0.67 (m, 2H), 2.10 (s, 3H), 2.83 (m, 1H), 3.62 (m, 2H), 4.18 (m, 2H), 4.60 (m, 1H), 5.69 (d, 1H), 6.97 (s, 1H), 7.02 (d, 1H), 7.51 (d, 1H), 7.61 (d, 1H), 7.79 (s, 1H), 7.87 (d, 1H), 8.01 (s, 1H), 8.43 (m, 1H); Mass Spectrum: $M+H^+$ 391.

The 2-amino-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-(3-hydroxyazetidin-1-yl)benzamide used for the starting material was prepared as follows:-

Using an analogous procedure to that described paragraph (A) in the portion of Example 13 which is concerned with the preparation of starting materials 3-hydroxyazetidine was reacted with *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-fluoro-2-nitrobenzamide to give *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-(3-hydroxyazetidin-1-yl)-2-nitrobenzamide; NMR Spectrum: ($DMSOd_6$) 0.55 (m, 2H), 0.67 (m, 2H), 2.28 (s, 3H), 2.84 (m, 1H), 3.79 (m, 2H), 4.29 (t, 2H), 4.63 (m, 1H), 5.82 (d, 1H), 6.48 (m, 2H), 7.28 (d, 1H), 7.56 (d, 1H), 7.95 (s, 1H), 8.04 (d, 1H), 8.37 (s, 1H), 9.87 (s, 1H); Mass Spectrum: $M+Na^+$ 433.

Using an analogous procedure to that described paragraph (B) in the portion of Example 13 which is concerned with the preparation of starting materials, *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-(3-hydroxyazetidin-1-yl)-2-nitrobenzamide was reduced to give the required starting material; Mass Spectrum: $M+H^+$ 381.

d) *N*-cyclopropyl-3-[6-(3R,5S)-3,5-dimethylpiperazin-1-yl)-4-oxoquinazoline-3(4*H*)-yl]-4-methylbenzamide gave the following data; NMR Spectrum: ($DMSOd_6$) 0.54 (m, 2H), 0.67 (m, 2H), 1.02 (m, 6H), 2.04 (m, 1H), 2.12 (s, 3H), 2.21 (t, 2H), 2.85 (m, 3H), 3.67 (d, 2H), 7.43 (s, 1H), 7.50 (d, 1H), 7.61 (s, 2H), 7.81 (s, 1H), 7.88 (d, 1H), 8.06 (s, 1H), 8.40 (m, 1H); Mass Spectrum: $M+H^+$ 432.

The 2-amino-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-[(3R,5S)-3,5-dimethylpiperazin-1-yl]benzamide used for the starting material was prepared as follows:-

Using an analogous procedure to that described paragraph (A) in the portion of Example 13 which is concerned with the preparation of starting materials *cis*-2,6 dimethylpiperazine was reacted with *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-fluoro-2-nitrobenzamide to give *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-[(3R,5S)-3,5-dimethylpipeazin-1-yl]-2-nitrobenzamide; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.69 (m, 2H), 1.03 (d, 6H), 2.28 (s, 3H), 2.40 (t, 2H), 2.79 (m, 3H), 3.94 (d, 2H), 7.05 (m, 2H), 7.28 (d, 1H), 7.55 (d, 1H), 8.01 (m, 2H), 8.36 (s, 1H), 9.87 (s, 1H); Mass Spectrum: $M+H^+$ 452.

Using an analogous procedure to that described paragraph (B) in the portion of Example 13 which is concerned with the preparation of starting materials, *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-[(3R,5S)-3,5-dimethylpipeazin-1-yl]-2-nitrobenzamide was reduced to give the required starting material; Mass Spectrum: $M+H^+$ 422.

e) *N*-cyclopropyl-3-[6-(3R,5S)-3,5-dimethylpiperazin-1-yl)-2-methyl-4-oxoquinazoline-3(4*H*)-yl]-4-methylbenzamide gave the following data; NMR Spectrum: (DMSOd_6) 0.56 (m, 2H), 0.67 (m, 2H), 1.02 (d, 6H), 2.01 (m, 6H), 2.18 (t, 3H), 2.84 (m, 3H), 3.62 (d, 2H), 7.33 (s, 1H), 7.53 (m, 3H), 7.72 (s, 1H), 7.86 (d, 1H), 8.39 (d, 1H); Mass Spectrum: M+H$^+$ 446.

The 2-amino-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-[(3R,5S)-3,5-dimethylpiperazin-1-yl]benzamide used for the starting material was prepared as described in note (d).

f) *N*-cyclopropyl-4-methyl-3-(4-oxo-6-piperidin-1-ylquinazoline-3(4*H*)-yl)benzamide gave the following data; NMR Spectrum: (DMSOd_6) 0.53 (m, 2H), 0.67 (m, 2H), 1.61 (m, 6H), 2.12 (s, 3H), 2.85 (m, 1H), 3.26 (m, 4H), 7.44 (s, 1H), 7.50 (d, 1H), 7.60 (s, 2H), 7.80 (s, 1H), 7.88 (d, 1H), 8.05 (s, 1H), 8.40 (d, 1H); Mass Spectrum: M+H$^+$ 403.

The 2-amino-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-piperidin-1-ylbenzamide used for the starting material was prepared as follows:-

Using an analogous procedure to that described paragraph (A) in the portion of Example 13 which is concerned with the preparation of starting materials piperidine was reacted with *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-fluoro-2-nitrobenzamide to give *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-2-nitro-5-piperidin-1-ylbenzamide; NMR Spectrum: (DMSOd_6) 0.56 (m, 2H), 0.68 (m, 2H), 1.60 (m, 6H), 2.30 (s, 3H), 2.82 (m, 1H), 3.52 (m, 4H), 7.02 (m, 2H), 7.27 (d, 1H), 7.55 (d, 1H), 7.96 (s, 1H), 8.02 (d, 1H), 8.39 (s, 1H), 9.95 (s, 1H); Mass Spectrum: M+H$^+$ 423.

Using an analogous procedure to that described paragraph (B) in the portion of Example 13 which is concerned with the preparation of starting materials, *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-2-nitro-5-piperidin-1-ylbenzamide was reduced to give the required starting material; Mass Spectrum: M+H$^+$ 393.

g) *N*-cyclopropyl-4-methyl-3-[6-(4-methylpiperidin-1-yl)-4-oxoquinazoline-3(4*H*)-yl)benzamide gave the following data; NMR Spectrum: (DMSOd_6) 0.53 (m, 2H), 0.67 (m, 2H), 0.92 (d, 3H), 1.23 (m, 2H), 1.54 (m, 1H), 1.71 (d, 2H), 2.11 (s, 3H), 2.80 (m, 3H), 3.81 (d, 2H), 7.45 (s, 1H), 7.50 (d, 1H), 7.60 (s, 2H), 7.80 (s, 1H), 7.88 (d, 1H), 8.04 (s, 1H), 8.41 (d, 1H); Mass Spectrum M+H$^+$ 417.

The 2-amino-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-(4-methylpiperidin-1-yl)benzamide used for the starting material was prepared as follows:-

Using an analogous procedure to that described in paragraph (A) in the portion of Example 13 which is concerned with the preparation of starting materials 4-methylpiperidine was reacted with *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-fluoro-2-nitrobenzamide to give *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-(4-methylpiperidin-1-yl)-2-nitrobenzamide; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.66 (m, 2H), 0.92 (d, 3H), 1.13 (m, 2H), 1.68 (m, 3H), 2.30 (s, 3H), 2.83 (m, 1H), 2.99 (t, 2H), 4.07 (d, 2H), 7.03 (m, 2H), 7.28 (d, 1H), 7.56 (d, 1H), 7.96 (s, 1H), 8.01 (d, 1H), 8.39 (s, 1H), 9.95 (s, 1H); Mass Spectrum: $M+H^+$ 437.

Using an analogous procedure to that described paragraph (B) in the portion of Example 13 which is concerned with the preparation of starting materials, *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-(4-methylpiperidin-1-yl)-2-nitrobenzamide was reduced to give the required starting material; Mass Spectrum: $M+H^+$ 407.

h) *N*-cyclopropyl-3-[6-{[2-(dimethylamino)ethyl]thio}-4-oxoquinazoline-3(4*H*)-yl]-4-methylbenzamide gave the following data; NMR Spectrum: ($DMSOd_6$) 0.55 (m, 2H), 0.67 (m, 2H), 2.13 (s, 3H), 2.17 (s, 6H), 2.52 (m, 2H), 2.84 (m, 1H), 3.18 (t, 2H), 7.51 (d, 1H), 7.70 (d, 1H), 7.82 (m, 2H), 7.89 (d, 1H), 8.01 (s, 1H), 8.25 (s, 1H), 8.42 (d, 1H); Mass Spectrum: $M+H^+$ 423.

The 2-amino-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-{[(2-(dimethylamino)ethyl]thio}benzamide used for the starting material was prepared as follows:-

Using an analogous procedure to that described paragraph (A) in the portion of Example 13 which is concerned with the preparation of starting materials 2-(dimethylamino)ethanethiol hydrochloride was reacted with *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-fluoro-2-nitrobenzamide to give *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-{[2-(dimethylamino)ethyl]thio}-2-nitrobenzamide; NMR Spectrum: ($DMSOd_6$) 0.57 (m, 2H), 0.67 (m, 2H), 2.20 (s, 6H), 2.30 (s, 3H), 2.57 (m, 2H), 2.83 (m, 1H), 3.28 (m, 2H), 7.31 (d, 1H), 7.59 (m, 3H), 7.93 (s, 1H), 8.08 (d, 1H), 8.38 (s, 1H), 10.14 (s, 1H); Mass Spectrum: $M+H^+$ 443.

Using an analogous procedure to that described paragraph (B) in the portion of Example 13 which is concerned with the preparation of starting materials, *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-{[2-(dimethylamino)ethyl]thio}-2-

nitrobenzamide was reduced to give the required starting material; Mass Spectrum: $M+H^+$ 413.

i) *N*-cyclopropyl-3-[6-[(3-hydroxy-2,2-dimethylpropyl)amino]-4-oxoquinazoline-3(4*H*)-yl]-4-methylbenzamide gave the following data; NMR Spectrum: ($DMSOd_6$) 0.53 (m, 2H), 0.67 (m, 2H), 0.90 (s, 6H), 2.10 (s, 3H), 2.48 (m, 4H), 2.84 (m, 1H), 2.95 (m, 2H), 3.21 (s, 2H), 4.58 (m, 1H), 6.06 (t, 1H), 7.18 (d, 1H), 7.28 (d, 1H), 7.48 (m, 2H), 7.78 (s, 1H), 7.87 (d, 1H), 7.92 (s, 1H), 8.40 (d, 1H); Mass Spectrum: $M+H^+$ 421.

The 2-amino-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-[(3-hydroxy-2,2-dimethylpropyl)amino]benzamide used for the starting material was prepared as follows:-

Using an analogous procedure to that described paragraph (A) in the portion of Example 13 which is concerned with the preparation of starting materials 3-amino-2,2-dimethylpropan-1-ol was reacted with *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-fluoro-2-nitrobenzamide to give *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-[(3-hydroxy-2,2-dimethylpropyl)amino]-2-nitrobenzamide; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.68 (m, 2H), 0.88 (s, 6H), 2.29 (s, 3H), 2.83 (m, 1H), 3.06 (d, 2H), 3.20 (s, 2H), 6.78 (m, 2H), 7.19 (s, 1H), 7.28 (d, 1H), 7.57 (d, 1H), 7.89 (s, 1H), 7.98 (d, 1H), 8.38 (d, 1H), 9.89 (s, 1H); Mass Spectrum: $M+Na^+$ 463.

Using an analogous procedure to that described paragraph (B) in the portion of Example 13 which is concerned with the preparation of starting materials, was *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-[(3-hydroxy-2,2-dimethylpropyl)amino]-2-nitrobenzamide reduced to give the required starting material; Mass Spectrum $M+H^+$ 411.

j) *N*-cyclopropyl-4-methyl-3-[2-methyl-6-(4-methyl-1,4-diazepan-1-yl)-4-oxoquinazoline-3(4*H*)-yl]benzamide gave the following data; NMR Spectrum: ($DMSOd_6$) 0.54 (m, 2H), 0.64 (m, 2H), 1.76 (m, 1H), 1.89 (m, 1H), 2.01 (s, 3H), 2.05 (s, 3H), 2.48 (m, 5H), 2.62 (m, 1H), 2.82 (m, 2H), 3.55 (m, 4H), 7.14 (s, 1H), 7.32 (d, 1H), 7.51 (d, 2H), 7.71 (s, 1H), 7.86 (d, 1H), 8.38 (s, 1H); Mass Spectrum: $M+H^+$ 446.

The 2-amino-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-(4-methyl-1,4-diazepan-1-yl)benzamide used for the starting material was prepared as follows:-

Using an analogous procedure to that described paragraph (A) in the portion of Example 13 which is concerned with the preparation of starting materials 1-methylhomopiperazine was reacted with *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-fluoro-2-nitrobenzamide to give *N*-{5-[(cyclopropylamino)carbonyl]-2-

methylphenyl}-5-(4-methyl-1,4-diazepan-1-yl)-2-nitrobenzamide; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.67 (m, 2H), 1.91 (m, 2H), 2.26 (s, 3H), 2.29 (s, 3H), 2.44 (m, 2H), 2.64 (m, 2H), 2.82 (m, 1H), 3.61 (m, 2H), 3.66 (m, 2H), 6.81 (s, 1H), 6.88 (d, 1H), 7.28 (d, 1H), 7.55 (d, 1H), 7.96 (s, 1H), 8.03 (d, 1H), 8.36 (s, 1H), 9.88 (s, 1H); Mass Spectrum: $M+H^+$ 452.

Using an analogous procedure to that described paragraph (B) in the portion of Example 13 which is concerned with the preparation of starting materials, *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-(4-methyl-1,4-diazepan-1-yl)-2-nitrobenzamide was reduced to give the required starting material; Mass Spectrum: $M+H^+$ 422.

Example 15

***N*-Cyclopropyl-4-methyl-3-[6-[(1-methylpiperidin-4-yl)oxy]-4-oxoquinazolin-3(4*H*)-yl]benzamide (AZ12233712)**

N-Cyclopropyl-4-methyl-3-[4-oxo-6-(piperidin-4-yloxy)quinazolin-3(4*H*)-yl]benzamide (0.3 g), iodomethane (0.044 ml) and potassium carbonate (0.397 g) were stirred in DMF (2 ml) for 18 hours at room temperature. The reaction mixture was diluted with ethyl acetate and the organic phase was washed with water (5 x), brine (2 x), dried (magnesium sulfate) and concentrated. The residue was dissolved in methylene chloride (2 ml) and stirred with PS-isocyanate resin (1.25 mmol/g) (0.28 g) and MP-carbonate (2.89 mmol/g) (0.488 g) for 19 hours and then filtered and concentrated to yield the title compound (0.129 g) as a cream solid; NMR Spectrum: ($DMSOd_6$) 0.55 (m, 2H), 0.69 (m, 2H), 1.70 (m, 2H), 1.97 (m, 2H), 2.13 (s, 3H), 2.19 (s, 3H), 2.22 (m, 2H), 2.60 (m, 2H), 2.85 (m, 1H), 4.55 (m, 1H), 7.51 (d, 1H), 7.52 (d, 1H), 7.59 (s, 1H), 7.72 (d, 1H), 7.82 (s, 1H), 7.90 (d, 1H), 8.17 (s, 1H), 8.42 (d, 1H); Mass Spectrum: $M+H^+$ 433.

A) The *N*-cyclopropyl-4-methyl-3-[4-oxo-6-(piperidin-4-yloxy)quinazolin-3(4*H*)-yl]benzamide used as starting material was prepared as follows:-

To a solution of *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-fluoro-2-nitrobenzamide (2.0 g) and *tert*-butyl 4-hydroxy-1-piperidinecarboxylate (1.69 g) in DMF (30 ml) was added sodium hydride (0.896 g of a 60% dispersion in oil) portion-wise (ice bath cooling). The reaction was stirred for 22 hours at room temperature under an atmosphere of argon. The reaction mixture was then poured into a saturated aqueous ammonium chloride solution (200 ml) and the resulting precipitate was collected by filtration, washed with diethyl

ether, and air dried to yield *tert*-butyl 4-{3-[({5-[(cyclopropylamino)carbonyl]-2-methylphenyl}amino)carbonyl]-4-nitrophenoxy}piperidine-1-carboxylate (2.76 g) as a yellow solid; NMR Spectrum: ($DMSOd_6$) 0.60 (m, 2H), 0.70 (m, 2H), 1.40 (s, 9H), 1.60 (m, 2H), 1.97 (m, 2H), 2.30 (s, 3H), 2.84 (m, 1H), 3.23 (m, 2H), 3.66 (m, 2H), 4.88 (m, 1H), 7.29 (m, 2H), 7.31 (s, 1H), 7.60 (d, 1H), 7.95 (s, 1H), 8.17 (d, 1H), 8.38 (d, 1H), 10.10 (s, 1H); Mass Spectrum: $M+Na^+$ 561.

B) *tert*-Butyl 4-{3-[({5-[(cyclopropylamino)carbonyl]-2-methylphenyl}amino)carbonyl]-4-nitrophenoxy}piperidine-1-carboxylate (4.03 g) and 10% Palladium on carbon (0.4 g) were stirred in ethanol (90 ml) under an atmosphere of hydrogen gas. After cessation of hydrogen uptake, the catalyst was removed by filtration through diatomaceous earth (Celite®). The filtrate was concentrated under reduced pressure to provide the crude *tert*-butyl 4-{4-amino-3-[({5-[(cyclopropylamino)carbonyl]-2-methylphenyl}amino)carbonyl]phenoxy}piperidine-1-carboxylate (3.50 g) which was used without further purification; NMR Spectrum: ($DMSOd_6$) 0.59 (m, 2H), 0.70 (m, 2H), 1.40 (s, 9H), 1.52 (m, 2H), 1.38 (m, 2H), 2.24 (s, 3H), 2.84 (m, 1H), 3.18 (m, 2H), 3.64 (m, 2H), 4.36 (m, 1H), 6.03 (s, 2H), 6.71 (d, 1H), 6.96 (d, 1H), 7.31 (d, 1H), 7.34 (s, 1H), 7.62 (d, 1H), 7.79 (s, 1H), 8.37 (d, 1H), 9.72 (s, 1H); Mass Spectrum: $M+Na^+$ 531.

C) Triethyl orthoformate (1.0 ml) was added to a stirred mixture of *tert*-butyl 4-{4-amino-3-[({5-[(cyclopropylamino)carbonyl]-2-methylphenyl}amino)carbonyl]phenoxy}piperidine-1-carboxylate (1.02 g) and glacial acetic acid (0.057 ml) in ethanol (15 ml). The mixture was heated to 80°C and stirred for 2 hours and then concentrated. The residue was diluted with ethyl acetate and washed with saturated aqueous $NaHCO_3$ solution, brine, dried (magnesium sulfate) and concentrated to provide *tert*-butyl 4-[(3-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4-oxo-3,4-dihydroquinazolin-6-yl)oxy]piperidine-1-carboxylate (0.994 g) as a light brown solid; NMR Spectrum: ($DMSOd_6$) 0.58 (m, 2H), 0.70 (m, 2H), 1.42 (s, 9H), 1.58 (m, 2H), 1.94 (m, 2H), 2.13 (s, 3H), 2.85 (m, 1H), 3.23 (m, 2H), 3.65 (m, 2H), 4.77 (m, 1H), 7.52 (d, 1H), 7.55 (d, 1H), 7.63 (s, 1H), 7.72 (d, 1H), 7.82 (s, 1H), 7.90 (d, 1H), 8.18 (s, 1H), 8.43 (d, 1H); Mass Spectrum: $M+H^+$ 519.

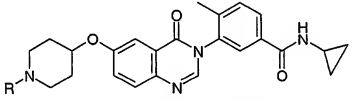
tert-Butyl 4-[(3-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4-oxo-3,4-dihydroquinazolin-6-yl)oxy]piperidine-1-carboxylate (3.42 g) was stirred in 4N HCl in dioxane (20 ml) and methanol (3 ml) at room temperature for 18 hours and then concentrated. The residue was purified by column chromatography on an ion exchange column (isolute

SCX-2 column from International Sorbent Technology Limited, Henoed, Mid-Glamorgan, UK) washing with methanol initially and then eluting with a 99:1 mixture of methanol and aqueous ammonia solution to give *N*-cyclopropyl-4-methyl-3-[4-oxo-6-(piperidin-4-yloxy)quinazolin-3(4*H*)-yl]benzamide (2.67 g) as a light brown solid; NMR Spectrum: ($DMSOd_6$) 0.54 (m, 2H), 0.69 (m, 2H), 1.50 (m, 2H), 1.95 (m, 2H), 2.15 (s, 3H), 2.60 (m, 2H), 2.85 (m, 1H), 2.95 (m, 2H), 4.59 (m, 1H), 7.51 (d, 1H), 7.52 (d, 1H), 7.59 (s, 1H), 7.71 (d, 1H), 7.82 (s, 1H), 7.90 (d, 1H), 8.18 (s, 1H), 8.42 (d, 1H); Mass Spectrum: $M+H^+$ 419.

Example 16

Using an analogous procedure to that described in Example 15, *N*-cyclopropyl-4-methyl-3-[4-oxo-6-(piperidin-4-yloxy)quinazolin-3(4*H*)-yl]benzamide was alkylated with the appropriate alkylating reagent to give the compounds described in Table 7.

Table 7



R	Method	Note
Ethyl (AZ12239933)	Ex 15	a
Isopropyl (AZ12240216)	Ex 15	b
2-Fluoroethyl (AZ12260236)	Ex 15	c
2-Methoxyethyl (AZ12260240)	Ex 15	d
2-Hydroxy-2-methylpropyl (AZ12299422)	_	e
(2*S*)-2-Hydroxypropyl (AZ12299429)	_	f
(2*R*)-2-Hydroxypropyl (AZ12299434)	_	g
2-Hydroxyethyl (AZ12301541)	Ex 15	h
Cyclopropylmethyl (AZ12091213)	Ex 15	i

Notes

a) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.54 (m, 2H), 0.69 (m, 2H), 1.00 (t, 3H), 1.69 (m, 2H), 1.97 (m, 2H), 2.12 (s, 3H), 2.22 (m, 2H), 2.33 (m, 2H), 2.67 (m, 2H), 2.83 (m, 1H), 4.54 (m, 1H), 7.51 (d, 1H), 7.52 (d, 1H), 7.59 (s,

1H), 7.72 (d, 1H), 7.81 (s, 1H), 7.89 (d, 1H), 8.17 (s, 1H), 8.41 (d, 1H); Mass Spectrum: M+H$^+$ 447.

b) The product gave the following data; NMR Spectrum: (DMSOd_6) 0.55 (m, 2H), 0.70 (m, 2H), 0.97 (s, 3H), 0.99 (s, 3H), 1.19 (m, 1H), 1.65 (m, 2H), 1.99 (m, 2H), 2.13 (s, 3H), 2.38 (m, 2H), 2.72 (m, 2H), 2.85 (m, 1H), 4.53 (m, 1H), 7.51 (d, 1H), 7.52 (d, 1H), 7.58 (s, 1H), 7.71 (d, 1H), 7.82 (s, 1H), 7.90 (d, 1H), 8.16 (s, 1H), 8.42 (d, 1H); Mass Spectrum: M+H$^+$ 461.

c) The product was purified by column chromatography on a silica column eluting initially with 10% methanol/ethyl acetate followed by 10% methanol/ethyl acetate + 1% aqueous ammonia solution. The product gave the following data; NMR Spectrum: (DMSOd_6) 0.54 (m, 2H), 0.70 (m, 2H), 1.70 (m, 2H), 1.99 (m, 2H), 2.14 (s, 3H), 2.38 (m, 2H), 2.64 (m, 2H), 2.76 (m, 2H), 2.85 (m, 1H), 4.54 (m, 2H), 4.59 (m, 1H), 7.53 (m, 2H), 7.60 (s, 1H), 7.72 (d, 1H), 7.82 (s, 1H), 7.90 (d, 1H), 8.18 (s, 1H), 8.43 (d, 1H); Mass Spectrum: M+H$^+$ 465.

d) The product was purified by column chromatography on a silica column eluting initially with 10% methanol/ethyl acetate followed by 10% methanol/ethyl acetate + 1% aqueous ammonia solution. The product gave the following data; NMR Spectrum: (DMSOd_6) 0.54 (m, 2H), 0.70 (m, 2H), 1.67 (m, 2H), 1.95 (m, 2H), 2.12 (s, 3H), 2.32 (m, 2H), 2.50 (m, 2H), 2.72 (m, 2H), 2.85 (m, 1H), 3.22 (s, 3H), 3.42 (t, 2H), 4.55 (m, 1H), 7.52 (m, 2H), 7.60 (s, 1H), 7.71 (d, 1H), 7.82 (s, 1H), 7.90 (d, 1H), 8.18 (s, 1H), 8.43 (d, 1H); Mass Spectrum: M+H$^+$ 477.

e) *N*-Cyclopropyl-4-methyl-3-[4-oxo-6-(piperidin-4-yloxy)quinazolin-3(4*H*)-yl]benzamide (0.25 g) and isobutylene oxide (0.159 ml) were stirred in a sealed tube in DMF (2 ml) at 80°C for 48 hours. The reaction mixture was diluted with ethyl acetate and washed with water (5 x), brine, dried (magnesium sulfate) and concentrated. Purification by column chromatography on a silica column eluting with 10% methanol/ethyl acetate gave *N*-cyclopropyl-3-[6-{[1-(2-hydroxy-2-methylpropyl)piperidin-4-yl]oxy}-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide (0.211 g) as a white foam solid; NMR Spectrum: (DMSOd_6) 0.55 (m, 2H), 0.70 (m, 2H), 1.10 (s, 6H), 1.69 (m, 2H), 1.95 (m, 2H), 2.13 (s, 3H), 2.22 (s, 2H), 2.43 (t, 2H), 2.85 (m, 3H), 4.01 (s, 1H), 4.54 (m, 1H), 7.52 (m, 2H), 7.59 (s, 1H), 7.72 (d, 1H), 7.83 (s, 1H), 7.91 (d, 1H), 8.18 (s, 1H), 8.42 (d, 1H); Mass Spectrum: M+H$^+$ 491.

f) *N*-Cyclopropyl-4-methyl-3-[4-oxo-6-(piperidin-4-yloxy)quinazolin-3(4*H*)-yl]benzamide (0.25 g) and (*S*)-(-)-propylene oxide (0.126 ml) were stirred in a sealed tube in DMF (2 ml) at 80°C for 21 hours. The reaction mixture was diluted with ethyl acetate and washed with water (5 x), brine, dried (magnesium sulfate) and concentrated. Purification by column chromatography on a silica column eluting with 10% methanol/ethyl acetate followed by 10% methanol/ethyl acetate + 1% aqueous ammonia solution gave *N*-cyclopropyl-3-[6-({1-[(2*S*)-2-hydroxypropyl]piperidin-4-yl}oxy)-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide (0.184 g) as a white foam solid; NMR Spectrum: ($DMSOd_6$) 0.55 (m, 2H), 0.69 (m, 2H), 1.03 (d, 3H), 1.60 (m, 2H), 1.97 (m, 2H), 2.14 (s, 3H), 2.18-2.37 (m, 4H), 2.72 (m, 2H), 2.85 (m, 1H), 3.74 (m, 1H), 4.22 (d, 1H), 4.55 (m, 1H), 7.52 (m, 2H), 7.59 (s, 1H), 7.73 (d, 1H), 7.83 (s, 1H), 7.90 (d, 1H), 8.19 (s, 1H), 8.43 (d, 1H); Mass Spectrum: $M+H^+$ 477.

g) *N*-Cyclopropyl-4-methyl-3-[4-oxo-6-(piperidin-4-yloxy)quinazolin-3(4*H*)-yl]benzamide (0.25 g) and (*R*)-(+)-propylene oxide (0.126 ml) were stirred in a sealed tube in DMF (2 ml) at 80°C for 21 hours. The reaction mixture was diluted with ethyl acetate and washed with water (5 x), brine, dried (magnesium sulfate) and concentrated. Purification by column chromatography on a silica column eluting with 10% methanol/ethyl acetate followed by 10% methanol/ethyl acetate + 1% aqueous ammonia solution gave *N*-cyclopropyl-3-[6-({1-[(2*R*)-2-hydroxypropyl]piperidin-4-yl}oxy)-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide (0.193 g) as a white foam solid; NMR Spectrum: ($DMSOd_6$) 0.55 (m, 2H), 0.69 (m, 2H), 1.03 (d, 3H), 1.60 (m, 2H), 1.97 (m, 2H), 2.14 (s, 3H), 2.18-2.37 (m, 4H), 2.72 (m, 2H), 2.85 (m, 1H), 3.74 (m, 1H), 4.22 (d, 1H), 4.55 (m, 1H), 7.52 (m, 2H), 7.59 (s, 1H), 7.73 (d, 1H), 7.83 (s, 1H), 7.90 (d, 1H), 8.19 (s, 1H), 8.43 (d, 1H); Mass Spectrum: $M+H^+$ 477.

h) Purification by column chromatography on a silica column eluting with 10% methanol/ethyl acetate followed by 10% methanol/ethyl acetate + 1% aqueous ammonia solution. The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.70 (m, 2H), 1.68 (m, 2H), 1.98 (m, 2H), 2.15 (s, 3H), 2.32 (m, 2H), 2.42 (t, 2H), 2.73 (m, 2H), 2.85 (m, 1H), 3.49 (m, 2H), 4.34 (t, 1H), 4.55 (m, 1H), 7.52 (m, 2H), 7.59 (s, 1H), 7.72 (d, 1H), 7.83 (s, 1H), 7.91 (d, 1H), 8.19 (s, 1H), 8.43 (d, 1H); Mass Spectrum: $M+H^+$ 463.

i) The product gave the following data; NMR Spectrum ($CDCl_3$) 0.56 (m, 4H), 0.88 (m, 5H), 1.90 (m, 2H), 2.10 (m, 2H), 2.22 (s, 3H), 2.29 (d, 2H), 2.41 (m, 2H), 2.86 (m, 3H), 4.50 (m, 1H), 6.49 (s, 1H), 7.41 (m, 2H), 7.68 (m, 3H), 7.78 (m, 1H), 7.86 (s, 1H); Mass Spectrum: $M+H^+$ 473.

Example 17

***N*-cyclopropyl-3-[6-[(1-cyclopropylpiperidine-4-yl)oxy]-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide (AZ12261875)**

Using an analogous procedure to that described in Example 1, 2-amino-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-[(1-cyclopropylpiperidine-4-yl)oxy] benzamide was reacted with triethylorthoformate. There was thus obtained the title compound (0.063 g); NMR Spectrum: ($DMSOd_6$) -0.01 (m, 2H), 0.12 (m, 2H), 0.27 (m, 2H), 0.40 (m, 2H), 1.34 (m, 3H), 1.65 (m, 2H), 1.84 (s, 3H), 2.18 (m, 2H), 2.53 (m, 3H), 4.28 (m, 1H), 7.23 (m, 2H), 7.29 (s, 1H), 7.43 (d, 1H), 7.53 (s, 1H), 7.60 (d, 1H), 7.89 (s, 1H), 8.14 (s, 1H); Mass Spectrum: $M+H^+$ 459.

The 2-amino-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-[(1-cyclopropylpiperidine-4-yl)oxy]benzamide used for the starting material was prepared as follows:-

A) *N*-benzyl-*N*-methyl-4-oxopiperidiumbromide (3.68 g) in water (6 ml) was added portionwise over 30 minutes to a stirred mixture of *N*-cyclopropylamine (0.404 g) and potassium carbonate in ethanol (15 ml) at 75°C. The mixture was stirred at 75°C for 45 minutes. The reaction mixture was evaporated, took up into water (20 ml) and extracted into methylene chloride. The organic extracts were combined and concentrated under reduced pressure and the residue was triturated with ether and the soluble fraction was isolated by evaporation (1.11 g) to give *N*-cyclopropyl-4-piperidone; NMR Spectrum: ($CDCl_3$) 0.50 (m, 4H), 1.73 (m, 1H), 2.40 (t, 4H), 2.91 (t, 4H).

B) Sodium borohydride (0.085 g) was added to a stirred solution of N-cyclopropyl-4-piperidone (0.312 g) in ethanol under an atmosphere of argon. The reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was evaporated, took up into water (20 ml) and extracted into methylene chloride. The organic extracts were combined and concentrated under reduced pressure to give N-cyclopropyl-4-piperidinol (0.298 g); NMR Spectrum: ($CDCl_3$) 0.50 (m, 4H), 1.35 (s, 1H), 1.55 (m, 2H), 1.86 (m, 2H) 2.34 (m, 2H), 2.89 (m, 2H), 3.70 (m, 1H).

C) Using an analogous procedure to that described paragraph (A) in the portion of Example 15 which is concerned with the preparation of starting material, *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-fluoro-2-nitrobenzamide was reacted with N-cyclopropyl-4-piperidol to give *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-[(1-cyclopropylpiperidine-4-yl)oxy]-2-nitrobenzamide; Mass Spectrum: $M+H^+$ 479.

Using an analogous procedure to that described paragraph (B) in the portion of Example 15 which is concerned with the preparation of starting material, *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-[(1-cyclopropylpiperidine-4-yl)oxy]-2-nitrobenzamide was reduced to2-amino-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-[(1-cyclopropylpiperidine-4-yl)oxy]benzamide; Mass Spectrum: $M+H^+$ 449.

Example 18

***N*-Cyclopropyl-4-methyl-3-[6-[(1-methylpyrrolidin-3-yl)oxy]-4-oxoquinazolin-3(4*H*)-yl]benzamide (AZ12257500)**

N-Cyclopropyl-4-methyl-3-[4-oxo-6-(pyrrolidin-4-yloxy)quinazolin-3(4*H*)-yl]benzamide (0.18 g), iodomethane (0.031 ml) and potassium carbonate (0.246 g) were stirred in DMA (1 ml) for 18 hours at room temperature. The reaction mixture was diluted with ethyl acetate and the organic phase was washed with water and concentrated. The residue was dissolved in ethyl acetate (2 ml) and triturated with *iso*-hexane and the resulting solid was filtered and dried under vacuum at 40°C. There was thus obtained the title compound (0.074 g); NMR Spectrum: ($DMSO-d_6$) 0.55 (m, 2H), 0.67 (m, 2H), 1.80 (m, 1H), 2.08 (m, 4H), 2.30 (m, 4H), 2.80 (m, 4H), 5.06 (s, 1H), 7.49 (m, 3H), 7.71 (d, 1H), 7.81 (s, 1H), 7.89 (d, 1H), 8.16 (s, 1H), 8.41 (s, 1H); Mass Spectrum: $M+H^+$ 419.

The *N*-cyclopropyl-4-methyl-3-[4-oxo-6-(pyrrolidine-3-yloxy)quinazolin-3(4*H*)-yl]benzamide used as starting material was prepared as follows:-

A) To a solution of *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-fluoro-2-nitrobenzamide (1.5 g) and *tert*-butyl 3-hydroxy-1-pyrrolidine-1-carboxylate (1.18 g) in DMF (5 ml) was added sodium hydride (0.67 g of a 60% dispersion in oil) portion-wise (ice bath cooling). The reaction was stirred for 22 hours at room temperature under an atmosphere of argon. The reaction mixture was then poured into water (200 ml) and adjusted to pH 7 with 1N HCl. The resulting precipitate was collected by filtration, washed with diethyl ether, and air dried under vacuum at 40°C There was thus obtained *tert*-butyl 3-{3-[({5-[(cyclopropylamino)carbonyl]-2-methylphenyl}amino)carbonyl]-4-nitrophenoxy}pyrrolidine-

1-carboxylate (2.29 g); NMR Spectrum: ($DMSOd_6$) 0.53 (m, 2H), 0.67 (m, 2H), 2.13 (s, 3H), 2.62 (m, 4H), 2.79 (m, 3H), 3.28 (m, 4H), 4.48 (m, 1H), 4.64 (m, 1H), 7.49 (m, 2H), 7.63 (s, 2H), 7.80 (s, 1H), 7.88 (m, 1H), 8.07 (s, 1H), 8.42 (d, 1H); Mass Spectrum: $M+H^+$ 450.

B) *tert*-Butyl 3-{3-[({5-[(cyclopropylamino)carbonyl]-2-methylphenyl}amino)carbonyl]-4-nitrophenoxy}pyrolidine-1-carboxylate (2.28 g) and 10% Palladium on carbon (0.2 g) were stirred in ethanol (90 ml) under an atmosphere of hydrogen gas at a pressure of 10 bar. After cessation of hydrogen uptake, the catalyst was removed by filtration through diatomaceous earth (Celite®). The filtrate was concentrated under reduced pressure to provide the crude *tert*-butyl 3-{4-amino-3-[({5-[(cyclopropylamino)carbonyl]-2-methylphenyl}amino)carbonyl]phenoxy}pyrrolidine-1-carboxylate (1.91 g) which was used without further purification; NMR Spectrum: ($DMSOd_6$) 0.55 (m, 2H), 0.67 (m, 2H), 1.39 (s, 9H), 2.03 (m, 2H), 2.24 (s, 3H), 2.82 (m, 1H), 3.39 (m, 4H), 4.86 (s, 1H), 6.04 (s, 2H), 6.70 (d, 1H), 6.91 (d, 1H), 7.30 (m, 2H), 7.60 (m, 1H), 7.76 (s, 1H), 8.35 (s, 1H), 9.73 (s, 1H); Mass Spectrum: $M+H^+$ 517.

C) Triethyl orthoformate (2.75 ml) was added to a stirred mixture of *tert*-butyl 3-{4-amino-3-[({5-[(cyclopropylamino)carbonyl]-2-methylphenyl}amino)carbonyl]phenoxy}pyrrolidine-1-carboxylate (1.9 g) and glacial acetic acid (0.138 ml) in ethanol (10 ml). The mixture was heated to 80°C and stirred for 16 hours. The reaction mixture was evaporated and the residue was purified by column chromatography on an ion exchange column (isolute SCX -2 column from International Sorbent Technology Limited, Henoed, Mid-Glamorgan, UK) using initially methanol and then a 99:1 mixture of methanol and aqueous ammonia solution. Fractions containing product were combined and evaporated and the residue was triturated with a mixture of ethyl acetate and *iso*-hexane. The resulting solid was filtered and dried under vacuum at 40°C. There was thus obtained *tert*-butyl 3-[(3-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4-oxo-3,4-dihydroquinazolin-6-yl)oxy]pyrrolidine-1-carboxylate (AZ12252294) (1.01 g); NMR Spectrum: ($DMSOd_6$) 0.54 (m, 2H), 0.67 (m, 2H), 0.82 (m, 2H), 1.39 (s, 9H), 2.14 (m, 5H), 2.84 (m, 1H), 3.35 (m, 1H), 3.60 (m, 1H), 5.18 (s, 1H), 7.52 (m, 3H), 7.73 (d, 1H), 7.82 (s, 1H), 7.88 (d, 1H), 8.19 (s, 1H), 8.42 (s, 1H); Mass Spectrum: $M+H^+$ 527.

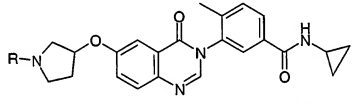
D) *tert*-Butyl-3-[(3-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4-oxo-3,4-dihydroquinazolin-6-yl)oxy]pyrrolidine-1-carboxylate (1.00 g) was stirred in 4N HCl in dioxane (6 ml) and methanol (2 ml) at room temperature for 18 hours and then concentrated.

The residue was purified by column chromatography on an ion exchange column (isolute SCX-2 column from International Sorbent Technology Limited, Henoed, Mid-Glamorgan, UK) washing with methanol initially and then eluting with a 99:1 mixture of methanol and aqueous ammonia solution. Fractions containing product were combined and evaporated. There was thus obtained cyclopropyl-4-methyl-3-[4-oxo-6-(pyrrolidine-3-yloxy)quinazolin-3(4*H*)-yl]benzamide (AZ12252295) (0.760 g) as a light orange solid; NMR Spectrum: ($DMSOd_6$) 0.54 (m, 2H), 0.68 (m, 2H), 2.13 (s, 3H), 2.21 (m, 2H), 2.84 (m, 1H), 3.45 (m, 4H), 5.34 (s, 1H), 7.54 (m, 2H), 7.62 (m, 1H), 7.76 (d, 1H), 7.83 (s, 1H), 7.91 (d, 1H), 8.21 (s, 1H), 8.48 (s, 1H); Mass Spectrum: $M+H^+$ 405.

Example 19

Using an analogous procedure to that described in Example 18, the *N*-Cyclopropyl-4-methyl-3-[4-oxo-6-(pyrrolidin-3-yloxy)quinazolin-3(4*H*)-yl]benzamide was reacted with the appropriate alkyl halide to give the compounds described in Table 8.

Table 8



R	Method	Note
Ethyl (AZ12257502)	Ex 18	a
Cyclopropylmethyl (AZ12257506)	Ex 18	b
Isopropyl (AZ12265614)	Ex 18	c

Notes

a) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.54 (m, 2H), 0.69 (m, 2H), 1.03 (m, 3H), 1.81 (m, 1H), 2.13 (s, 3H), 2.35 (m, 3H), 2.48 (m, 1H), 2.78 (m, 4H), 5.01 (s, 1H), 7.48 (m, 3H), 7.70 (d, 1H), 7.82 (s, 1H), 7.88 (d, 1H), 8.18 (s, 1H), 8.41 (s, 1H); Mass Spectrum: $M+H^+$ 433.

b) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.00 (m, 2H), 0.37 (m, 2H), 0.48 (m, 2H), 0.61 (m, 2H), 1.75 (m, 1H), 2.06 (s, 3H), 2.21 (m, 3H), 2.34 (m, 1H),

2.73 (m, 4H), 4.94 (m, 1H), 7.42 (m, 3H), 7.66 (d, 1H), 7.74 (s, 1H), 7.82 (d, 1H), 8.11 (s, 1H), 8.35 (d, 1H); Mass Spectrum: $M+H^+$ 459.

c) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.54 (m, 2H), 0.69 (m, 2H), 1.01 (d, 6H), 1.81 (m, 1H), 2.13 (s, 3H), 2.27 (m, 1H), 2.38 (m, 1H), 2.74 (m, 2H), 2.86 (m, 2H), 5.00 (m, 1H), 7.48 (m, 3H), 7.72 (d, 1H), 7.82 (s, 1H), 7.89 (d, 1H), 8.16 (s, 1H), 8.41 (d, 1H); Mass Spectrum: $M+H^+$ 447.

Example 20

***N*-Cyclopropyl-4-methyl-3-[4-oxo-6-[(3S)-pyrrolidin-3-yloxy]quinazolin-3(4*H*)-yl]benzamide (AZ12272557)**

Using an analogous procedure to that described paragraph (D) in the portion of Example 18 which is concerned with the preparation of starting materials *tert*-Butyl (3S)-3-[(3-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4-oxo-3,4-dihydroquinazolin-6-yl)oxy]pyrrolidine-1-carboxylate was reacted with 4N HCl in dioxane. There was thus obtained the title compound; NMR Spectrum: ($DMSOd_6$) 0.54 (m, 2H), 0.68 (m, 2H), 1.80 (m, 1H), 2.04 (m, 1H), 2.11 (s, 3H), 2.84 (m, 4H), 3.08 (m, 2H), 4.98 (m, 1H), 7.48 (m, 3H), 7.71 (d, 1H), 7.81 (s, 1H), 7.89 (d, 1H), 8.16 (s, 1H), 8.42 (d, 1H); Mass Spectrum: $M+H^+$ 405.

The *tert*-Butyl (3S)-3-[(3-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4-oxo-3,4-dihydroquinazolin-6-yl)oxy]pyrrolidine-1-carboxylate used for the starting material was prepared as follows:-

Using an analogous procedure to that described paragraph (A) in the portion of Example 18 which is concerned with the preparation of starting material, *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-fluoro-2-nitrobenzamide was reacted with *tert*-butyl (3S)-hydroxy-1-pyrrolidine-1-carboxylate to give *tert*-butyl (3S)-3-{3-[({5-[(cyclopropylamino)carbonyl]-2-methylphenyl}amino)carbonyl]-4-nitrophenoxy}pyrrolidine-1-carboxylate; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.67 (m, 2H), 1.40 (s, 9H), 2.15 (m, 2H), 2.30 (s, 3H), 2.82 (m, 1H), 3.42 (m, 4H), 5.27 (s, 1H), 7.27 (m, 3H), 7.59 (d, 1H), 7.95 (s, 1H), 8.16 (d, 1H), 8.37 (s, 1H), 10.10 (s, 1H); Mass Spectrum: $M+H^+$ 425.

Using an analogous procedure to that described paragraph (B) in the portion of Example 18 which is concerned with the preparation of starting material, *tert*-butyl (3S)-3-{3-[({5-[(cyclopropylamino)carbonyl]-2-methylphenyl}amino)carbonyl]-4-nitrophenoxy}pyrrolidine-1-carboxylate was reduced to *tert*-butyl (3S)-3-{4-amino-3-[({5-

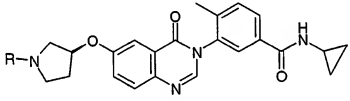
[(cyclopropylamino)carbonyl]-2-methylphenyl}amino)carbonyl]phenoxy}pyrrolidine-1-carboxylate; Mass Spectrum: M+Na$^+$ 517.

Using an analogous procedure to that described paragraph (C) in the portion of Example 18 which is concerned with the preparation of starting material, *tert*-butyl (3S)-3-{4-amino-3-[({5-[(cyclopropylamino)carbonyl]-2-methylphenyl}amino)carbonyl]phenoxy}pyrrolidine-1-carboxylate was reacted with triethylorthoformate to give *tert*-butyl (3S)-3-[(3-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4-oxo-3,4-dihydroquinazolin-6-yl)oxy]pyrrolidine-1-carboxylate; NMR Spectrum: (DMSOd_6) 0.53 (m, 2H), 0.68 (m, 2H), 1.40 (s, 9H), 2.14 (m, 5H), 2.84 (m, 1H), 3.50 (m, 4H), 5.20 (s, 1H), 7.52 (m, 3H), 7.72 (d, 1H), 7.81 (s, 1H), 7.88 (m, 1H), 8.17 (s, 1H), 8.41 (s, 1H); Mass Spectrum: M+H$^+$ 527.

Example 21

Using an analogous procedure to that described in Example 18, the *N*-Cyclopropyl-4-methyl-3-[4-oxo-6-[(3S)-pyrrolidin-3-yloxy]quinazolin-3(4*H*)-yl]benzamide was reacted with the appropriate alkyl halide to give the compounds described in Table 9.

Table 9



R	Method	Note
Methyl (AZ12274765)	Ex 18	a
Ethyl (AZ12274766)	Ex 18	b
Cyclopropylmethyl (AZ12274777)	Ex 18	c
Isopropyl (AZ12274780)	Ex 18	d

Notes

a) The product gave the following data; NMR Spectrum: (DMSOd_6) 0.54 (m, 2H), 0.67 (m, 2H), 1.81 (m, 1H), 2.13 (s, 3H), 2.30 (m, 4H), 2.76 (m, 5H), 5.01 (m, 1H), 7.48 (m, 3H), 7.70 (d, 1H), 7.81 (s, 1H), 7.88 (d, 1H), 8.17 (s, 1H), 8.40 (s, 1H); Mass Spectrum: M+H$^+$ 419.

b) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.55 (m, 2H), 0.68 (m, 2H), 1.03 (m, 3H), 1.80 (m, 1H), 2.12 (s, 3H), 2.35 (m, 4H), 2.77 (m, 4H), 5.00 (m, 1H), 7.48 (m, 3H), 7.71 (d, 1H), 7.81 (s, 1H), 7.88 (d, 1H), 8.17 (s, 1H), 8.41 (s, 1H); Mass Spectrum: $M+H^+$ 433.

c) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.00 (m, 2H), 0.36 (m, 2H), 0.47 (m, 2H), 0.61 (m, 2H), 0.76 (m, 1H), 1.74 (m, 1H), 2.06 (s, 3H), 2.21 (m, 2H), 2.34 (m, 2H), 2.74 (m, 4H), 4.95 (m, 1H), 7.43 (m, 3H), 7.64 (d, 1H), 7.76 (s, 1H), 7.83 (d, 1H), 8.11 (s, 1H), 8.36 (s, 1H); Mass Spectrum: $M+H^+$ 459.

d) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.55 (m, 2H), 0.67 (m, 2H), 1.01 (m, 6H), 1.81 (m, 1H), 2.14 (s, 3H), 2.33 (m, 2H), 2.80 (m, 5H), 4.99 (m, 1H), 7.48 (m, 3H), 7.70 (d, 1H), 7.82 (s, 1H), 7.89 (d, 1H), 8.17 (s, 1H), 8.42 (s, 1H); Mass Spectrum: $M+H^+$ 447.

Example 22

***N*-Cyclopropyl-4-methyl-3-[4-oxo-6-[(3R)-pyrrolidin-3-yloxy]quinazolin-3(4*H*)-yl]benzamide (AZ12277780)**

Using an analogous procedure to that described paragraph (D) in the portion of Example 18 which is concerned with the preparation of starting materials *tert*-Butyl (3R)-3-[(3-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4-oxo-3,4-dihydroquinazolin-6-yl)oxy]pyrrolidine-1-carboxylate was reacted with 4N HCl in dioxane. There was thus obtained the title compound; NMR Spectrum: ($DMSOd_6$) 0.52 (m, 2H), 0.66 (m, 2H), 1.79 (m, 1H), 2.04 (m, 1H), 2.14 (s, 3H), 2.84 (m, 4H), 3.07 (m, 1H), 5.00 (m, 1H), 7.48 (m, 3H), 7.71 (d, 1H), 7.82 (s, 1H), 7.89 (d, 1H), 8.18 (s, 1H), 8.42 (s, 1H); Mass Spectrum: $M+H^+$ 405.

The *tert*-Butyl (3R)-3-[(3-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4-oxo-3,4-dihydroquinazolin-6-yl)oxy]pyrrolidine-1-carboxylate used for the starting material was prepared as follows:-

Using an analogous procedure to that described paragraph (A) in the portion of Example 18 which is concerned with the preparation of starting material, *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-fluoro-2-nitrobenzamide was reacted with *tert*-butyl (3R)-hydroxy-1-pyrrolidine-1-carboxylate to give *tert*-butyl (3R)-3-{3-[({5-[(cyclopropylamino)carbonyl]-2-methylphenyl}amino)carbonyl]-4-nitrophenoxy}pyrrolidine-1-carboxylate; NMR Spectrum: ($DMSOd_6$) 0.57 (m, 2H), 0.67 (m, 2H), 1.38 (s, 9H), 2.13 (m,

2H), 2.31 (s, 3H), 2.84 (m, 1H), 3.50 (m, 4H), 5.27 (m, 1H), 7.26 (m, 3H), 7.60 (d, 1H), 7.94 (s, 1H), 8.17 (d, 1H), 8.37 (s, 1H), 10.13 (s, 1H); Mass Spectrum: $M+H^+$ 523.

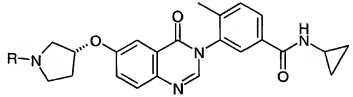
Using an analogous procedure to that described paragraph (B) in the portion of Example 18 which is concerned with the preparation of starting material, *tert*-butyl (3R)-3-{3-[({5-[(cyclopropylamino)carbonyl]-2-methylphenyl}amino)carbonyl]-4-nitrophenoxy}pyrrolidine-1-carboxylate was reduced to *tert*-butyl (3R)-3-{4-amino-3-[({5-[(cyclopropylamino)carbonyl]-2-methylphenyl}amino)carbonyl]phenoxy}pyrrolidine-1-carboxylate; Mass Spectrum: $M+Na^+$ 517.

Using an analogous procedure to that described paragraph (C) in the portion of Example 18 which is concerned with the preparation of starting material, *tert*-butyl (3R)-3-{4-amino-3-[({5-[(cyclopropylamino)carbonyl]-2-methylphenyl}amino)carbonyl]phenoxy}pyrrolidine-1-carboxylate was reacted with triethylorthoformate to give *tert*-butyl (3R)-3-[(3-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4-oxo-3,4-dihydroquinazolin-6-yl)oxy]pyrrolidine-1-carboxylate; NMR Spectrum: ($DMSOd_6$) 0.54 (m, 2H), 0.68 (m, 2H), 1.39 (s, 9H), 2.15 (m, 5H), 2.85 (m, 1H), 3.50 (m, 4H), 5.19 (m, 1H), 7.54 (m, 3H), 7.72 (d, 1H), 7.83 (s, 1H), 7.89 (d, 1H), 8.19 (s, 1H), 8.41 (s, 1H); Mass Spectrum: $M+Na^+$ 527.

Example 23

Using an analogous procedure to that described in Example 22, the *N*-Cyclopropyl-4-methyl-3-[4-oxo-6-[(3R)-pyrrolidin-3-yloxy]quinazolin-3(4*H*)-yl]benzamide was reacted with the appropriate alkyl halide to give the compounds described in Table 10.

Table 10



R	Method	Note
Methyl (AZ12280225)	Ex 22	a
Ethyl (AZ12280237)	Ex 22	b
Cyclopropylmethyl (AZ12280243)	Ex 22	c
Isopropyl (AZ12280244)	Ex 22	d

Notes

a) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.54 (m, 2H), 0.68 (m, 2H), 1.80 (m, 1H), 2.09 (m, 4H), 2.32 (m, 4H), 2.76 (m, 4H), 5.01 (m, 1H), 7.48 (m, 3H), 7.71 (d, 1H), 7.83 (s, 1H), 7.89 (d, 1H), 8.17 (s, 1H), 8.41 (s, 1H); Mass Spectrum: $M+H^+$ 419.

b) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.54 (m, 2H), 0.67 (m, 2H), 1.02 (t, 3H), 1.81 (m, 1H), 2.12 (s, 3H), 2.34 (m, 4H), 2.79 (m, 4H), 5.01 (m, 1H), 7.49 (m, 3H), 7.71 (d, 1H), 7.81 (s, 1H), 7.88 (d, 1H), 8.17 (s, 1H), 8.40 (s, 1H); Mass Spectrum: $M+H^+$ 433.

c) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.00 (m, 2H), 0.36 (m, 2H), 0.47 (m, 2H), 0.62 (m, 2H), 0.78 (m, 1H), 1.74 (m, 1H), 2.06 (s, 3H), 2.24 (m, 3H), 2.35 (m, 1H), 2.74 (m, 4H), 4.94 (m, 1H), 7.42 (m, 3H), 7.65 (d, 1H), 7.76 (s, 1H), 7.82 (d, 1H), 8.10 (s, 1H), 8.34 (s, 1H); Mass Spectrum: $M+H^+$ 459.

d) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.54 (m, 2H), 0.68 (m, 2H), 1.00 (m, 6H), 1.80 (m, 1H), 2.13 (s, 3H), 2.32 (m, 3H), 2.81 (m, 4H), 4.97 (m, 1H), 7.49 (m, 3H), 7.71 (d, 1H), 7.82 (s, 1H), 7.89 (d, 1H), 8.16 (s, 1H), 8.42 (s, 1H); Mass Spectrum: $M+H^+$ 447.

Example 24

***N*-Cyclopropyl-3-[6-[2-(dimethylamino)ethoxy]-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide (AZ12260955)**

N-Cyclopropyl-3-(6-hydroxy-4-oxoquinazolin-3(4*H*)-yl)-4-methylbenzamide (0.15 g), 2-dimethylaminoethyl chloride hydrochloride (0.084 g), potassium carbonate (0.62 g), and sodium iodide (0.007 g) were stirred in acetone (9 ml) at 60°C for 18 hours. The reaction mixture was filtered, the solids washed with acetone, and the filtrate was concentrated. The residue was dissolved in ethyl acetate and washed with 2N NaOH solution, brine, dried (magnesium sulfate) and concentrated. Purification by column chromatography on a silica column eluting with 10% methanol/ethyl acetate + 1% aqueous ammonia solution gave the title compound (0.159 g) as a white solid; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.70 (m, 2H), 2.13 (s, 3H), 2.23 (s, 6H), 2.68 (t, 2H), 2.85 (m, 1H), 4.19 (t, 2H), 7.52 (m, 2H), 7.60 (s, 1H), 7.72 (d, 1H), 7.83 (s, 1H), 7.91 (d, 1H), 8.19 (s, 1H), 8.42 (d, 1H); Mass Spectrum: $M+H^+$ 407.

The *N*-cyclopropyl-3-(6-hydroxy-4-oxoquinazolin-3(4*H*)-yl)-4-methylbenzamide used as starting material was prepared as follows:-

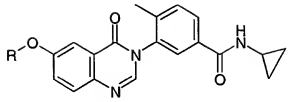
A) A stirred mixture of 2-amino-5-methoxybenzoic acid (10 g), trimethyl orthoformate (13.1 ml), and acetic acid (0.34 ml) in toluene (240 ml) was heated under reflux for 6 hours. 3-Amino-*N*-cyclopropyl-4-methylbenzamide (10.23 g) was added to the reaction mixture and stirring continued at reflux for 16 hours. The reaction mixture was allowed to cool and then was diluted with ethyl acetate. The organic solution was then washed with 1N HCl solution, 2N NaOH solution (x 2), brine, dried (magnesium sulfate), and concentrated to a cream coloured foam/solid. Recrystallisation from ethyl acetate gave *N*-cyclopropyl-3-(6-methoxy-4-oxoquinazolin-3(4*H*)-yl)-4-methylbenzamide (AZ12239719) (11.33 g) as a white solid; NMR Spectrum: ($DMSOd_6$) 0.62 (m, 2H), 0.75 (m, 2H), 2.19 (s, 3H), 2.90 (m, 1H), 3.95 (s, 3H), 7.56 (m, 2H), 7.63 (s, 1H), 7.78 (d, 1H), 7.89 (s, 1H), 7.95 (d, 1H), 8.23 (s, 1H), 8.48 (d, 1H); Mass Spectrum: $M+H^+$ 350.

B) To a solution of *N*-Cyclopropyl-3-(6-methoxy-4-oxoquinazolin-3(4*H*)-yl)-4-methylbenzamide (4.62 g) in methylene chloride (90 ml) was added 1M boron tribromide in methylene chloride (53 ml) and stirred for 20 hours. The reaction was quenched with water and then diluted with 2N NaOH solution until the solid dissolved. The aqueous layer was washed with methylene chloride (2 x) and then acidified to pH 1 with 2N HCl solution and extracted with ethyl acetate (3 x). The combined organic extracts were concentrated and the solid was dried by azeotropic removal of water using toluene to yield *N*-cyclopropyl-3-(6-hydroxy-4-oxoquinazolin-3(4*H*)-yl)-4-methylbenzamide (AZ12266450) (3.06 g) as a white solid; NMR Spectrum: ($DMSOd_6$) 0.55 (m, 2H), 0.70 (m, 2H), 2.12 (s, 3H), 2.85 (m, 1H), 7.35 (d, 1H), 7.50 (s, 1H), 7.52 (d, 1H), 7.66 (d, 1H), 7.82 (s, 1H), 7.90 (d, 1H), 8.11 (s, 1H), 8.42 (d, 1H), 10.20 (broad s, 1H); Mass Spectrum: $M+H^+$ 336.

Example 25

Using an analogous procedure to that described in Example 24, *N*-cyclopropyl-3-(6-hydroxy-4-oxoquinazolin-3(4*H*)-yl)-4-methylbenzamide was alkylated with the appropriate alkylating reagent to give the compounds described in Table 11.

Table 11



R	Method	Note
2-Pyrrolidin-1-ylethoxy (AZ12264643)	Ex 24	a
2-Morpholin-4-ylethoxy (AZ12264644)	Ex 24	b
2-Piperidin-1-ylethoxy (AZ12264646)	Ex 24	c
3-(Dimethylamino)propoxy (AZ12265022)	Ex 24	d
Pyridin-2-ylmethoxy (AZ12255234)	-	e
2-(Dimethylamino)-2-oxoethoxy (AZ12280334)	-	f
3-Piperidin-1-ylpropoxy (AZ12278325)	Ex 24	g
2-(1*H*-Pyrrol-1-yl)ethoxy (AZ12278393)	Ex 24	h
3-Pyrrolidin-1-ylpropoxy (AZ12278395)	Ex 24	i
2-(Dimethylamino)-2-methylpropoxy (AZ12278397)	Ex 24	j
3-(1*H*-Pyrrol-1-yl)propoxy (AZ12278400)	Ex 24	k
3-(4-Methylpiperazin-1-yl)propoxy (AZ12282575)	Ex 24	l
(R/S)-(1-Methylpiperidin-3-yl)methoxy (AZ12282576)	Ex 24	m
2-(1*H*-Imidazol-1-yl)ethoxy (AZ12282577)	Ex 24	n
2-(2-Oxoimidazolidin-1-yl)ethoxy (AZ12282578)	Ex 24	o
(R/S)-1-Methylpiperidin-2-yl)methoxy (AZ12282579)	Ex 24	p
(1-Methyl-1H-imidazol-2-yl)methoxy (AZ12282580)	Ex 24	q
2-(Ethylthio)ethoxy (AZ12301803)	Ex 24	r
2-(*tert*-Butylamino)ethoxy (AZ12301804)	Ex 24	s
(R/S)-3-(Dimethylamino)-2-methylpropoxy (AZ12301805)	Ex 24	t
(4-Methylmorpholin-2-yl)methoxy (AZ12302321)	-	u

Notes

a) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.70 (m, 2H), 1.70 (m, 4H), 2.14 (s, 3H), 2.53 (m, 4H), 2.83-2.90 (m, 3H), 4.20 (t, 2H),

7.52 (m, 2H), 7.60 (s, 1H), 7.73 (d, 1H), 7.83 (s, 1H), 7.91 (d, 1H), 8.19 (s, 1H), 8.43 (d, 1H); Mass Spectrum: $M+H^+$ 433.

b) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.54 (m, 2H), 0.70 (m, 2H), 2.20 (s, 3H), 2.50 (m, 4H), 2.73 (t, 2H), 2.85 (m, 1H), 3.58 (m, 4H), 4.23 (t, 2H), 7.52 (m, 2H), 7.60 (s, 1H), 7.72 (d, 1H), 7.83 (s, 1H), 7.90 (d, 1H), 8.19 (s, 1H), 8.42 (d, 1H); Mass Spectrum: $M+H^+$ 449.

c) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.55 (m, 2H), 0.70 (m, 2H), 1.38 (m, 2H), 1.50 (m, 4H), 2.12 (s, 3H), 2.43 (m, 4H), 2.69 (t, 2H), 2.84 (m, 1H), 4.20 (m, 2H), 7.51 (m, 2H), 7.60 (s, 1H), 7.71 (d, 1H), 7.82 (s, 1H), 7.91 (d, 1H), 8.19 (s, 1H), 8.42 (d, 1H); Mass Spectrum: $M+H^+$ 447.

d) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.69 (m, 2H), 1.90 (m, 2H), 2.11 (s, 3H), 2.15 (s, 6H), 2.39 (t, 2H), 2.85 (m, 1H), 4.13 (t, 2H), 7.51 (d, 1H), 7.53 (d, 1H), 7.58 (s, 1H), 7.72 (d, 1H), 7.84 (s, 1H), 7.91 (d, 1H), 8.18 (s, 1H), 8.43 (d, 1H); Mass Spectrum: $M+H^+$ 421.

e) Purification by column chromatography on a silica column eluting with 5% methanol/methylene chloride followed by trituration with methanol. The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.70 (m, 2H), 2.12 (s, 3H), 2.86 (m, 1H), 5.34 (s, 2H), 7.37 (m, 1H), 7.52 (d, 1H), 7.58 (d, 1H), 7.63 (d, 1H), 7.68 (s, 1H), 7.77 (d, 1H), 7.83 (s, 1H), 7.87 (m, 1H), 7.90 (d, 1H), 8.20 (s, 1H), 8.41 (d, 1H), 8.60 (d, 1H); Mass Spectrum: $M+H^+$ 427.

f) Purification by column chromatography on a silica column eluting with 10% methanol/ethyl acetate. The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.69 (m, 2H), 2.14 (s, 3H), 2.85 (m, 4H), 3.02 (s, 3H), 5.00 (s, 2H), 7.53 (m, 3H), 7.72 (d, 1H), 7.83 (s, 1H), 7.91 (d, 1H), 8.19 (s, 1H), 8.43 (d, 1H); Mass Spectrum: $M+H^+$ 421.

g) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.70 (m, 2H), 1.38 (m, 2H), 1.50 (m, 4H), 1.92 (m, 2H), 2.17 (s, 3H), 2.38 (m, 6H), 2.86 (m, 1H), 4.15 (t, 2H), 7.51 (m, 2H), 7.59 (s, 1H), 7.72 (d, 1H), 7.86 (s, 1H), 7.91 (d, 1H), 8.21 (s, 1H), 8.43 (d, 1H); Mass Spectrum: $M+H^+$ 461.

h) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.69 (m, 2H), 2.17 (s, 3H), 2.87 (m, 1H), 4.35 (m, 4H), 6.07 (s, 2H), 6.90 (s, 2H), 7.51 (m,

2H), 7.58 (d, 1H), 7.73 (d, 1H), 7.85 (s, 1H), 7.91 (d, 1H), 8.21 (s, 1H), 8.43 (d, 1H); Mass Spectrum: $M+H^+$ 429.

i) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.70 (m, 2H), 1.70 (m, 4H), 1.96 (m, 2H), 2.19 (s, 3H), 2.58 (m, 4H), 2.86 (m, 1H), 4.17 (m, 2H), 7.52 (m, 2H), 7.59 (d, 1H), 7.73 (d, 1H), 7.85 (s, 1H), 7.91 (d, 1H), 8.20 (s, 1H), 8.43 (d, 1H); Mass Spectrum: $M+H^+$ 477.

j) The product gave the following data; Mass Spectrum: $M+H^+$ 435.

k) The product gave the following data; NMR Spectrum: ($CDCl_3$) 0.59 (m, 2H), 0.84 (m, 2H), 1.66 (s, 1H), 2.24 (s, 3H), 2.29 (m, 2H), 2.87 (m, 1H), 4.02 (m, 2H), 4.13 (m, 2H), 6.15 (s, 2H), 6.37 (s, 1H), 6.66 (s, 2H), 7.41 (m, 2H), 7.63 (d, 2H), 7.70 (d, 1H), 7.78 (d, 1H), 7.86 (s, 1H); Mass Spectrum: $M+H^+$ 443.

l) The product gave the following data; Mass Spectrum: $M+H^+$ 498.

m) The product gave the following data; Mass Spectrum: $M+H^+$ 447.

n) The product gave the following data; Mass Spectrum: $M+H^+$ 520.

o) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.69 (m, 2H), 2.18 (s, 3H), 2.86 (m, 1H), 3.17 (d, 2H), 3.25 (m, 2H), 3.48 (m, 2H), 4.06 (m, 1H), 4.23 (m, 2H), 6.38 (s, 1H), 7.53 (m, 2H), 7.64 (s, 1H), 7.74 (d, 1H), 7.87 (s, 1H), 7.91 (d, 1H), 8.20 (s, 1H), 8.42 (d, 1H); Mass Spectrum: $M+H^+$ 448.

p) The product gave the following data; Mass Spectrum: $M+H^+$ 447.

q) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.54 (m, 2H), 0.67 (m, 2H), 2.17 (s, 3H), 2.84 (m, 1H), 3.73 (s, 3H), 5.32 (s, 2H), 6.90 (s, 1H), 7.20 (s, 1H), 7.55 (m, 2H), 7.73 (m, 1H), 7.81 (m, 2H), 7.89 (m, 1H), 8.20 (s, 1H), 8.43 (d, 1H); Mass Spectrum: $M+H^+$ 430.

r) The product gave the following data; Mass Spectrum: $2M+H^+$ 847.

s) The product gave the following data; Mass Spectrum: $M+H^+$ 435.

t) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.57 (m, 2H), 0.71 (m, 2H), 0.87 (m, 1H), 1.14 (d, 3H), 1.32 (m, 1H), 2.19 (s, 3H), 2.82 (m, 6H), 3.07 (m, 1H), 3.27 (m, 1H), 4.11 (m, 2H), 7.55 (m, 2H), 7.65 (s, 1H), 7.76 (d, 1H), 7.88 (s, 1H), 7.92 (d, 1H), 8.24 (s, 1H), 8.48 (d, 1H); Mass Spectrum: $M+H^+$ 435.

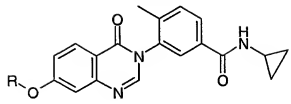
u) *N*-Cyclopropyl-3-(6-hydroxy-4-oxoquinazolin-3(4*H*)-yl)-4-methylbenzamide (1.01 g), *tert*-butyl 2-{[(methylsulfonyl)oxy]methyl}morpholine-4-carboxylate (1.15 g) and K_2CO_3 were suspended in DMA (10 ml) and heated to 110 °C for 18hrs. After cooling

to room temperatrure, water (100 ml) was added and extracted with ethyl acetate (2 x 100ml). The pooled organic layers were washed saturated $NaHCO_3$ solution (2 x 100ml), brine (100 ml) and dried (magnesium sulphate) and concentrated. Purification by column chromatography on a silica column eluting *iso*-hexane/ethyl acetate (1:4) to ethyl acetate gave the *tert*-butyl 2-{[(3-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4-oxo-3,4-dihydroquinazolin-6-yl)oxy]methyl}morpholine-4-carboxylate (1.05 g); NMR Spectrum: ($DMSOd_6$) 0.62 (m, 4H), 1.40 (s, 9H), 2.13 (s, 3H), 2.83 (m, 3H), 3.46 (m, 1H), 3.72 (m, 2H), 3.91 (m, 2H), 4.16 (m, 2H), 7.52 (m, 2H), 7.59 (d, 1H), 7.72 (d, 1H), 7.83 (d, 1H), 7.89 (m, 1H), 8.18 (s, 1H), 8.42 (d, 1H); Mass Spectrum: $M+H^+$ 535. To a stirred solution of *tert*-Butyl 2-{[(3-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4-oxo-3,4-dihydroquinazolin-6-yl)oxy]methyl}morpholine-4-carboxylate (0.53 g) in formic acid (10 ml) was added 38% aqueous formaldehyde (0.75 ml) and heated to 90 °C for 18 hours. On cooling to room temperature, water (20 ml) was added and the solution poured onto an ion exchange column (isolute SCX-2 column from International Sorbent Technology Limited, Henoed, Mid-Glamorgan, UK). The column was washed with water (2 x 50 ml), methanol (2 x 50 ml) and the product eluted with 2N ammonia in methanol. The fractions containing product were evaporated *in vacuo*. Purification by column chromatography on a silica column eluting 10% methanol/ethyl acetate to 2% 7N ammonina in MeOH/10% methanol/ethyl acetate gave the title compound; NMR Spectrum: ($DMSOd_6$) 0.64 (m, 4H), 1.97 (m, 2H), 2.13 (s, 3H), 2.19 (s, 3H), 2.59 (m, 1H), 2.83 (m, 2H), 3.54 (m, 1H), 3.82 (m, 2H), 4.11 (m, 2H), 7.53 (m, 3H), 7.71 (d, 1H), 7.82 (m, 1H), 7.90 (m, 1H), 8.17 (m, 1H), 8.42 (d, 1H); Mass Spectrum: $M+H^+$ 449.

Example 26

Using an analogous procedure to that described in Example 24, *N*-cyclopropyl-3-(7-hydroxy-4-oxoquinazolin-3(4*H*)-yl)-4-methylbenzamide was alkylated with the appropriate alkylating reagent to give the compounds described in Table 12.

Table 12



R	Method	Note
2-Morpholin-4-ylethoxy (AZ12299220)	Ex 24	a
3-(Dimethylamino)propoxy (AZ12299219)	Ex 24	b

Notes

a) The product gave the following data; Mass Spectrum: $M+H^+$ 429.

b) The product gave the following data; Mass Spectrum: $M+H^+$ 421.

Example 27

***N*-cyclopropyl-3-[6-(2-hydroxy-2-methyl-3-pyrrolidin-1-ylpropoxy)-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide** (AZ12199678)

To a solution of the crude 3-[(3-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4-oxo-3,4-dihydroquinazolin-6-yl)oxy]-2-hydroxy-2-methylpropyl 4-methylbenzenesulfonate (0.2 g) in anhydrous DMF (10 ml) was added potassium carbonate (0.1 g) followed by pyrrolidine (0.15 g) and the mixture stirred at room temperature for 18 hours. The mixture was concentrated and purification by preparative HPLC provided the title compound as a gum (50mg); NMR Spectrum: ($CDCl_3$) 0.60 (m, 2H), 0.90 (m, 2H), 1.20 (m, 1H), 1.40 (s, 3H), 1.80 (m, 4H), 2.20 (s, 3H), 2.75 (m, 6H), 4.20 (m, 2H), 6.40 (s, 1H), 7.50 (m, 2H), 7.70 (m, 3H), 7.80 (d, 1H), 7.90 (s, 1H); Mass Spectrum: $M+H^+$ 477.

The 3-[(3-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4-oxo-3,4-dihydroquinazolin-6-yl)oxy]-2-hydroxy-2-methylpropyl 4-methylbenzenesulfonate used as starting material was prepared as follows:-

To a solution of methylallyl alcohol (3.6 ml) in anhydrous DMA (200 ml) was added sodium hydride (60% dispersion in oil, 6.7g) and the solution stirred for 1 hour. *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-fluoro-2-nitrobenzamide (10 g) was added and the mixture stirred at room temperature for 18 hours. The mixture was poured into 1N citric acid (300 ml) and the precipitated solid filtered off under reduced pressure and dried in the vacuum oven to give *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-[(2-

methylprop-2-en-1-yl)oxy]-2-nitrobenzamide as an orange solid (8.73 g); NMR Spectrum (DMSOd6) 0.6 (m, 2H), 0.7 (m, 2H), 1.9 (s, 3H), 2.3 (s, 1H), 2.9 (m, 1H), 4.7 (s, 2H), 5.1 (s, 1H), 5.2 (s, 1H), 7.2 (m, 3H), 7.6 (d, 1H), 7.9 (s, 1H), 8.2 (d, 1H), 8.4 (m, 1H), 10.1 (s, 1H); Mass Spectrum: M-H$^+$ 408.

To a solution of *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-[(2-methylprop-2-en-1-yl)oxy]-2-nitrobenzamide (8.73 g) in methanol (250 ml) was added a saturated solution of copper acetate in water (80 ml). Sodium borohydride (4.3 g) was added portionwise and the mixture stirred for a further 1 hour at room temperature. Ethyl acetate (300 ml) was added and the mixture washed with aqueous sodium hydrogen carbonate (200 ml). The combined aqueous extracts were extracted with ethyl acetate (2 x 200 ml), the resulting organics washed with brine (100 ml) and dried (magnesium sulfate) and Concentrated to give the crude 2-amino-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-[(2-methylprop-2-en-1-yl)oxy]benzamide (3.6 g) as an oil which was used directly in the next step.

A solution of 2-amino-*N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-[(2-methylprop-2-en-1-yl)oxy]benzamide (3.6 g), triethylorthoformate (4.6 ml) and acetic acid (0.6 ml) in ethanol (50 ml) was heated at reflux for 18 hours. The reaction was cooled to room temperaute and concentrated. The residue was partitioned between aqueous potassium carbonate solution (50 ml) and ethyl acetate (200 ml). The organic extracts were washed with brine (100 ml), dried (magnesium sulfate) and concentrated to give the crude *N*-cyclopropyl-4-methyl-3-[6-[(2-methylprop-2-en-1-yl)oxy]-4-oxoquinazolin-3(4*H*)-yl]benzamide as an oil (2.5 g) which was used directly in the next step.

To a solution of *N*-cyclopropyl-4-methyl-3-[6-[(2-methylprop-2-en-1-yl)oxy]-4-oxoquinazolin-3(4*H*)-yl]benzamide (1.76 g) in acetone/water (4:1, 40 ml) was added *N*-methylmorpholine-N-oxide (2.1 g) followed by a solution of osmium tetroxide in 2-methyl-2-propanol (2.5% solution, 1.2 ml). After 18 hours sodium bisulfite (0.1 g) was added and the mixture stirred for a further 1 hour. The crude mixture was poured into water (20 ml) and extracted into ethyl acetate (300 ml). The combined organic extracts were washed with brine (100 ml), dried (magnesium sulfate) and concentrated. Purification by preparative HPLC provided *N*-cyclopropyl-3-[6-(2,3-dihydroxy-2-methylpropoxy)-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide (AZ12197886) (0.5 g); NMR Spectrum: ($CDCl_3$) 0.45 (m, 2H), 0.75 (m, 2H), 1.32 (s, 3H), 1.70 (m, 2H), 2.10 (s, 3H), 2.70 (m, 1H), 3.60 (d, 1H), 3.70 (m, 1H), 3.90

(m, 2H), 6.70 (d, 1H), 7.30 (m, 1H), 7.45 (m, 1H), 7.50 (m, 2H), 7.70 (m, 1H), 7.90 (s, 1H), 7.95 (t, 1H); Mass Spectrum: $M+H^+$ 424. Further elution provided *N*-cyclopropyl-3-(6-isobutoxy-4-oxoquinazolin-3(4*H*)-yl)-4-methylbenzamide (AZ12198379) as a clear oil (70mg); NMR Spectrum ($CDCl_3$) 0.50 (m, 2H), 0.90 (m, 2H), 1.10 (s, 3H), 1.15 (s, 3H), 2.15 (m, 1H), 2.20 (s, 3H), 2.90 (m, 1H), 3.90 (d, 2H), 6.60 (s, 1H), 7.40 (m, 2H), 7.60 (d, 1H), 7.70 (m, 2H), 7.80 (m, 1H), 7.90 (s, 1H); Mass Spectrum $M+H^+$ 392.

To a solution of *N*-cyclopropyl-3-[6-(2,3-dihydroxy-2-methylpropoxy)-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide (0.2 g) in pyridine (10 ml) was added *p*-toluenesulfonylchloride (0.18 g) followed by 4-dimethylaminopyridine (cat.) and the mixture heated at 60°C for 18 hours. The reaction mixture was concentrated under reduced pressure and redissolved in ethyl acetate. The organics were washed with 1N citric acid, brine, dried (magnesium sulfate) and concentrated to give the crude 3-[(3-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4-oxo-3,4-dihydroquinazolin-6-yl)oxy]-2-hydroxy-2-methylpropyl 4-methylbenzenesulfonate (0.21g) which was used without further purification.

Example 28

N-Cyclopropyl-4-methyl-3-[6-[2-(1,4-oxazepan-4-yl)ethoxy]-4-oxoquinazolin-3(4*H*)-yl]benzamide (AZ12272886)

3-[6-(2-Chloroethoxy)-4-oxoquinazolin-3(4*H*)-yl]-*N*-cyclopropyl-4-methylbenzamide (0.15 g), potassium iodide (0.13 g), 1,4-oxazepane hydrochloride (0.32 g), and *N,N*-diisopropylethylamine (0.8 ml) were stirred in DMA (3 ml) and heated under microwave irradiation conditions (Personal Chemistry Emrys Optimizer with 300W magnetron) at 140°C for 1 hour. The reaction mixture was diluted with ethyl acetate and washed with water (5 x), brine (2 x), dried (magnesium sulfate) and concentrated. Purification by column chromatography on a silica column eluting with 10% methanol/ethyl acetate gave the title compound (0.111 g) as a white solid; NMR Spectrum: ($DMSOd_6$) 0.55 (m, 2H), 0.70 (m, 2H), 1.80 (m, 2H), 2.13 (s, 3H), 2.76 (m, 4H), 2.86 (m, 1H), 2.93 (t, 2H), 3.60 (t, 2H), 3.65 (t, 2H), 4.20 (m, 2H), 7.52 (m, 2H), 7.60 (s, 1H), 7.72 (d, 1H), 7.83 (s, 1H), 7.91 (d, 1H), 8.19 (s, 1H), 8.43 (d, 1H); Mass Spectrum: $M+H^+$ 463.

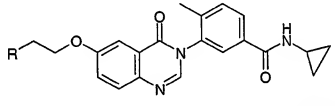
The 3-[6-(2-chloroethoxy)-4-oxoquinazolin-3(4*H*)-yl]-*N*-cyclopropyl-4-methylbenzamide used as starting material was prepared as follows:-

N-Cyclopropyl-3-(6-hydroxy-4-oxoquinazolin-3(4*H*)-yl)-4-methylbenzamide (0.621 g), 1-bromo-2-chloroethane (0.772 ml) and potassium carbonate (2.56 g) were stirred in DMF (25 ml) at 50°C for 24 hours. The reaction mixture was diluted with ethyl acetate and washed with water (5 x), brine (2 x), dried (magnesium sulfate) and concentrated. Purification by column chromatography on a silica column eluting with 70-80% ethyl acetate/hexane gave 3-[6-(2-chloroethoxy)-4-oxoquinazolin-3(4*H*)-yl]-*N*-cyclopropyl-4-methylbenzamide (0.46 g) as a white solid; NMR Spectrum: ($DMSOd_6$) 0.55 (m, 2H), 0.70 (m, 2H), 2.12 (s, 3H), 2.35 (m, 1H), 3.98 (t, 2H), 4.41 (t, 2H), 7.52 (d, 1H), 7.55 (d, 1H), 7.61 (s, 1H), 7.75 (d, 1H), 7.85 (s, 1H), 7.91 (d, 1H), 8.20 (s, 1H), 8.44 (d, 1H); Mass Spectrum: $M+H^+$ 398.

Example 29

Using an analogous procedure to that described in Example 28, 3-[6-(2-chloroethoxy)-4-oxoquinazolin-3(4*H*)-yl]-*N*-cyclopropyl-4-methylbenzamide was reacted with the appropriate amine to give the compounds described in Table 13.

Table 13



R	Method	Note
4-Isopropylpiperazin-1-yl (AZ12267339)	Ex 28	a
4,4-Difluoropiperidin-1-yl (AZ12267342)	Ex 28	b
(3*R*)-3-Fluoropyrrolidin-1-yl (AZ12267376)	Ex 28	c
Methyl(pyridin-2-ylmethyl)amino (AZ12272889)	Ex 28	d
(2-Methoxyethyl)(methyl)amino (AZ12273405)	Ex 28	e
Azetidin-1-yl (AZ12264648)	–	f
2-Thiomorpholin-4-ylethoxy (AZ12285351)	Ex 28	g
2-(4-Hydroxypiperidin-1-yl)ethoxy (AZ12285352)	Ex 28	h
2-[(Cyclobutylmethyl)(methyl)amino]ethoxy (AZ12285353)	Ex 28	i
2-{Methyl[2-(methylsulfonyl)ethyl]amino}ethoxy (AZ12285354)	Ex 28	j
2-{Methyl[(1-methyl-1H-pyrazol-4-yl)methyl]amino}ethoxy (AZ12285355)	Ex 28	k

2-[(2*S*)-2-(Hydroxymethyl)pyrrolidin-1-yl]ethoxy (AZ12301798)	Ex 28	l
2-[(2*S*)-2-(Methoxymethyl)pyrrolidin-1-yl]ethoxy (AZ12301799)	Ex 28	m
2-[Isopropyl(methyl)amino]ethoxy (AZ12301800)	Ex 28	n
2-[Isopropyl(2-methoxyethyl)amino]ethoxy (AZ12301801)	Ex 28	o
(2-*tert*-Butoxyethyl)(methyl)amino]ethoxy (AZ12301925)	Ex 28	p

Notes

a) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.54 (m, 2H), 0.69 (m, 2H), 0.93 (d, 6H), 2.11 (s, 3H), 2.40-2.50 (m, 8H), 2.56 (m, 1H), 2.70 (t, 2H), 2.85 (m, 1H), 4.20 (m, 2H), 7.52 (m, 2H), 7.59 (s, 1H), 7.72 (d, 1H), 7.83 (s, 1H), 7.91 (d, 1H), 8.20 (s, 1H), 8.48 (d, 1H); Mass Spectrum: $M+H^+$ 490.

b) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.54 (m, 2H), 0.69 (m, 2H), 1.90-2.00 (m, 4H), 2.12 (s, 3H), 2.63 (m, 4H), 2.82-2.88 (m, 3H), 4.24 (m, 2H), 7.52 (m, 2H), 7.61 (s, 1H), 7.72 (d, 1H), 7.84 (s, 1H), 7.91 (d, 1H), 8.20 (s, 1H), 8.48 (d, 1H); Mass Spectrum: $M+H^+$ 483.

c) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.54 (m, 2H), 0.70 (m, 2H), 1.80-1.95 (m, 1H), 2.06-2.21 (m, 1H), 2.14 (s, 3H), 2.41-2.55 (m, 2H), 2.67-2.79 (m, 1H), 2.83-2.98 (m, 4H), 4.22 (m, 2H), 5.11-5.29 (m, 1H), 7.52 (m, 2H), 7.60 (s, 1H), 7.73 (d, 1H), 7.83 (s, 1H), 7.91 (d, 1H), 8.19 (s, 1H), 8.42 (d, 1H); Mass Spectrum: $M+H^+$ 451.

d) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.60 (m, 2H), 0.74 (m, 2H), 2.20 (s, 3H), 2.38 (s, 3H), 2.93 (m, 3H), 3.79 (s, 2H), 4.32 (m, 2H), 7.29 (m, 1H), 7.51-7.61 (m, 3H), 7.66 (s, 1H), 7.79 (d, 1H), 7.81 (m, 1H), 7.89 (s, 1H), 7.96 (d, 1H), 8.23 (s, 1H), 8.48 (d, 1H), 8.52 (d, 1H); Mass Spectrum: $M+H^+$ 484.

e) The hydrochloride salt of the product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.69 (m, 2H), 2.13 (s, 3H), 2.85 (m, 1H), 2.90 (d, 3H), 3.32 (s, 3H), 3.36 (m, 1H), 3.43-3.60 (m, 2H), 3.68 (m, 1H), 3.72 (t, 2H), 4.55 (broad t, 2H), 7.52 (d, 1H), 7.59 (d, 1H), 7.68 (s, 1H), 7.79 (d, 1H), 7.87 (s, 1H), 7.91 (d, 1H), 8.25 (s, 1H), 8.49 (d, 1H); Mass Spectrum: $M+H^+$ 451.

f) 3-[6-(2-Chloroethoxy)-4-oxoquinazolin-3(4*H*)-yl]-*N*-cyclopropyl-4-methylbenzamide (0.2 g), azetidine (0.1 ml) and potassium carbonate (0.7 g) were stirred in DMA (3 ml) and heated under microwave irradiation conditions (Personal Chemistry Emrys

Optimizer with 300W magnetron) at 120°C for 30 minutes. The reaction mixture was diluted with ethyl acetate and washed with water (5 x), brine (2 x), dried (magnesium sulfate) and concentrated. Purification by column chromatography on a silica column eluting with 10% methanol/ethyl acetate + 1% aqueous ammonia solution gave 3-[6-(2-azetidin-1-ylethoxy)-4-oxoquinazolin-3(4*H*)-yl]-*N*-cyclopropyl-4-methylbenzamide (0.138 g) as a white solid; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.70 (m, 2H), 1.99 (m, 2H), 2.14 (s, 3H), 2.75 (t, 2H), 2.85 (m, 1H), 3.20 (t, 4H), 4.03 (t, 2H), 7.47-7.57 (m, 3H), 7.71 (d, 1H), 7.82 (s, 1H), 7.90 (d, 1H), 8.19 (s, 1H), 8.43 (d, 1H); Mass Spectrum: $M+H^+$ 419.

g) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.70 (m, 2H), 2.14 (m, 3H), 2.62 (m, 4H), 2.78 (m, 4H), 2.86 (m, 1H), 3.28 (m, 2H), 4.21 (m, 2H), 7.52 (m, 2H), 7.61 (m, 1H), 7.74 (d, 1H), 7.85 (m, 1H), 7.91 (m, 1H), 8.20 (s, 1H), 8.43 (d, 1H); Mass Spectrum: $M+H^+$ 465.

h) The product gave the following data; Mass Spectrum: $M+H^+$ 463.

i) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.55 (m, 2H), 0.70 (m, 2H), 1.93 - 1.60 (m, 3H), 2.03 (m, 2H), 2.18 (s, 3H), 2.35 (m, 3H), 2.59 (m, 3H), 2.88 (m, 3H), 4.26 (m, 2H), 7.53 (m, 2H), 7.64 (s, 1H), 7.75 (d, 1H), 7.85 (s, 1H), 7.91 (d, 1H), 8.21 (s, 1H), 8.44 (d, 1H); Mass Spectrum: $M+H^+$ 461

j) The product gave the following data; Mass Spectrum: $M+H^+$ 499.

k) The product gave the following data; Mass Spectrum: $M+H^+$ 487.

l) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.70 (m, 2H), 2.09 - 1.69 (m, 3H), 2.18 (s, 3H), 2.87 (m, 1H), 3.29 (m, 1H), 3.63 (m, 4H), 3.83 (m, 2H), 4.50 (m, 2H), 7.56 (m, 2H), 7.70 (s, 1H), 7.79 (d, 1H), 7.88 (s, 1H), 7.91 (d, 1H), 8.27 (s, 1H), 8.46 (d, 1H), 9.46 (s, 1H); Mass Spectrum: $M+H^+$ 463

m) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.58 (m, 2H), 0.71 (m, 2H), 1.68 (m, 1H), 2.09 - 1.86 (m, 2H), 2.18 (s, 3H), 2.85 (m, 1H), 3.37 (s, 3H), 3.63 (m, 5H), 3.83 (m, 3H), 4.53 (m, 2H), 7.54 (m, 1H), 7.60 (m, 1H), 7.69 (s, 1H), 7.79 (d, 1H), 7.89 (s, 1H), 7.92 (d, 1H), 8.27 (s, 1H), 8.49 (d, 1H); Mass Spectrum: $M+H^+$ 477.

n) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.70 (m, 2H), 1.28 (m, 6H), 2.18 (s, 3H), 2.84 (m, 4H), 3.45 (m, 1H), 3.64 (m, 2H), 4.49

(m, 2H), 7.56 (m, 2H), 7.71 (s, 1H), 7.79 (d, 1H), 7.86 (s, 1H), 7.92 (d, 1H), 8.26 (s, 1H), 8.46 (d, 1H); Mass Spectrum: $M+H^+$ 435.

o) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.54 (m, 2H), 0.70 (m, 2H), 0.91 (m, 6H), 2.13 (s, 3H), 2.67 (m, 2H), 2.82 (m, 3H), 2.94 (m, 1H), 3.22 (s, 3H), 3.33 (m, 2H), 4.08 (m, 2H), 7.56 (m, 2H), 7.71 (s, 1H), 7.79 (d, 1H), 7.86 (s, 1H), 7.92 (d, 1H), 8.26 (s, 1H), 8.46 (d, 1H); Mass Spectrum: $M+H^+$ 479

p) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.57 (m, 2H), 0.70 (m, 2H), 1.12 (s, 9H), 2.57 (m, 2H), 2.84 (m, 3H), 3.30 (s, 3H), 3.40 (m, 2H), 4.19 (m, 2H), 7.52 (m, 2H), 7.60 (s, 1H), 7.73 (d, 1H), 7.84 (s, 1H), 7.91 (d, 1H), 8.19 (s, 1H), 8.43 (d, 1H); Mass Spectrum: $M+H^+$ 493.

Example 30

_N_-cyclopropyl-4-methyl-3-[4-oxo-6-(3-thiomorpholin-4-ylpropoxy)quinazolin-3(4*H*)-yl]benzamide (AZ12313091)

3-[6-(2-Chloropropoxyoxy)-4-oxoquinazolin-3(4*H*)-yl]-*N*-cyclopropyl-4-methylbenzamide (0.23g), thiomorpholine (0.37g) and potassium iodide (0.2g) were stirred in DMA (3 ml) and heated under microwave irradiation conditions (Personal Chemistry Emrys Optimizer with 300W magnetron) for 30 mins at 120°C. The reaction mixture was filtered, washed with ethyl acetate and the filtrate concentrated. Purification by column chromatography on a silica column eluting with a 0% to 30% MeOH / EtOAc gradient gave the title compound (0.19 g) as a white solid; Mass Spectrum: $M+H^+$ 479.

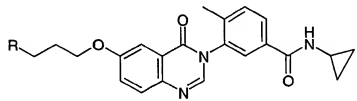
The 3-[6-(3-chloropropoxy)-4-oxoquinazolin-3(4*H*)-yl]-*N*-cyclopropyl-4-methylbenzamide used as starting material was prepared as follows:-

N-Cyclopropyl-3-(6-hydroxy-4-oxoquinazolin-3(4*H*)-yl)-4-methylbenzamide (5 g), 1-bromo-3-chloropropane (7.4 ml) and potassium carbonate (20.6 g) were stirred in DMF (175 ml) at 50°C for 24 hours. The reaction mixture was diluted with ethyl acetate and washed with water (5 x), brine (2 x), dried (magnesium sulfate) and concentrated. Purification by column chromatography on a silica column eluting with 70-80% ethyl acetate/hexane gave 3-[6-(2-chloropropoxy)-4-oxoquinazolin-3(4*H*)-yl]-*N*-cyclopropyl-4-methylbenzamide (3.28 g) as a white solid; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.69 (m, 2H), 2.14 (s, 3H), 2.22 (m, 2H), 2.85 (m, 1H), 3.81 (t, 2H), 4.23 (m, 2H), 7.52 (m, 2H), 7.60 (s, 1H), 7.74 (d, 1H), 7.84 (s, 1H), 7.90 (d, 1H), 8.20 (s, 1H), 8.43 (d, 1H); Mass Spectrum: $M+H^+$ 412.

Example 31

Using an analogous procedure to that described in Example 30, 3-[6-(2-chloropropoxy)-4-oxoquinazolin-3(4*H*)-yl]-*N*-cyclopropyl-4-methylbenzamide was reacted with the appropriate amine to give the compounds described in Table 14.

Table 14



R	Method	Note
(3R)-3-hydroxypyrrolidin-1-yl (AZ12313092)	Ex 30	a
4-hydroxypiperidin-1-yl (AZ12313093)	Ex 30	b
(2-methoxyethyl)(methyl)amino (AZ12313094)	Ex 30	c
(3-furylmethyl)(methyl)amino (AZ12313095)	Ex 30	d
(cyclobutylmethyl)(methyl)amino (AZ12313096)	Ex 30	e

Notes

a) The product gave the following data; NMR Spectrum: (DMSOd_6) 0.50 (m, 1H), 0.80 (m, 2H), 1.40 (t, 1H), 2.00 (m, 6H), 2.60 (s, 1H), 2.80 (m, 4H), 3.00 (s, 5H), 4.20 (m, 2H), 4.50 (m, 2H), 6.50 (d, 1H), 7.38 (m, 1H), 7.43 (d, 1H), 7.62 (m, 1H), 7.67 (m, 1H), 7.76 (m, 1H), 7.84 (d, 1H); Mass Spectrum: M+H$^+$ 463.

b) The product gave the following data; Mass Spectrum: M+H$^+$ 477.

c) The product gave the following data; Mass Spectrum: M+H$^+$ 465.

d) The product gave the following data; NMR Spectrum: (DMSOd_6) 0.60 (m, 2H), 0.80 (m, 2H), 2.20 (m, 5H), 2.50 (s, 3H), 2.80 (m, 3H), 3.30 (s, 2H), 4.00 (s, 1H), 4.20 (t, 2H), 6.50 (s, 1), 7.33 (m, 1H), 7.41 (m, 2H), 7.48 (s, 1H), 7.60 (d, 1H), 7.65 (m, 2H), 7.78 (m, 1H), 7.85 (s, 1H); Mass Spectrum: M+H$^+$ 487.

e) The product gave the following data; Mass Spectrum: M+H$^+$ 475.

Example 32

***N*-Cyclopropyl-4-methyl-3-[6-{2-[(methylsulfonyl)amino]ethoxy}-4-oxoquinazolin-3(4*H*)-yl]benzamide (AZ12280338)**

3-[6-(2-Aminoethoxy)-4-oxoquinazolin-3(4*H*)-yl]-*N*-cyclopropyl-4-methylbenzamide (0.1 g), methanesulfonyl chloride (0.027 ml), and triethylamine (0.074 ml) were stirred in methylene chloride (2 ml) under an atmosphere of argon for 2 hours at room temperature. The reaction mixture was diluted with ethyl acetate and washed with water (2 x), brine, dried (magnesium sulfate) and concentrated. Purification by column chromatography on a silica column eluting with 10% methanol/ethyl acetate gave the title compound (0.106 g) as a white solid; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.69 (m, 2H), 2.15 (s, 3H), 2.85 (m, 1H), 2.96 (s, 3H), 3.41 (m, 2H), 4.19 (t, 2H), 7.30 (t, 1H), 7.54 (m, 2H), 7.60 (s, 1H), 7.75 (d, 1H), 7.84 (s, 1H), 7.91 (d, 1H), 8.20 (s, 1H), 8.43 (d, 1H); Mass Spectrum: $M+H^+$ 457.

The 3-[6-(2-aminoethoxy)-4-oxoquinazolin-3(4*H*)-yl]-*N*-cyclopropyl-4-methylbenzamide used as starting material was prepared as follows:-

N-Cyclopropyl-3-(6-hydroxy-4-oxoquinazolin-3(4*H*)-yl)-4-methylbenzamide (0.621 g), 2-(*tert*-butoxycarbonylamino)ethyl bromide (0.5 g), potassium carbonate (2.06 g), and potassium iodide (0.025 g) were stirred in DMF (10 ml) at 60°C for 16 hours. The reaction mixture was diluted with ethyl acetate and washed with water (5 x), brine (2 x), dried (magnesium sulfate) and concentrated. The resulting solid was dissolved in a solution of 4N HCl in dioxane (4 ml) and methanol (3 ml) and stirred at room temperature for 16 hours. The precipitate was collected by filtration and washed with ethyl acetate. Purification by column chromatography on an ion exchange column (isolute SCX-2 column from International Sorbent Technology Limited, Henoed, Mid-Glamorgan, UK) washing with methanol initially and then eluting with a 99:1 mixture of methanol and aqueous ammonia solution gave 3-[6-(2-aminoethoxy)-4-oxoquinazolin-3(4*H*)-yl]-*N*-cyclopropyl-4-methylbenzamide (AZ12278502) (0.343 g) as a white solid; NMR Spectrum: ($DMSOd_6$) 0.55 (m, 2H), 0.69 (m, 2H), 1.81 (broad s, 2H), 2.14 (s, 3H), 2.87 (m, 1H), 2.93 (t, 2H), 4.08 (m, 2H), 7.52 (m, 2H), 7.59 (s, 1H), 7.73 (d, 1H), 7.84 (s, 1H), 7.91 (d, 1H), 8.19 (s, 1H), 8.43 (d, 1H); Mass Spectrum: $M+H^+$ 379.

Example 33

3-[6-[2-(Acetylamino)ethoxy]-4-oxoquinazolin-3(4*H*)-yl]-*N*-cyclopropyl-4-methylbenzamide (AZ12280339)

3-[6-(2-Aminoethoxy)-4-oxoquinazolin-3(4*H*)-yl]-*N*-cyclopropyl-4-methylbenzamide (0.1 g), acetyl chloride (0.025 ml), and triethylamine (0.074 ml) were stirred in methylene chloride (2 ml) under an atmosphere of argon for 2 hours at room temperature. The reaction mixture was diluted with ethyl acetate and washed with water (2 x), brine, dried (magnesium sulfate) and concentrated. Purification by column chromatography on a silica column eluting with 10% methanol/ethyl acetate gave the title compound (0.067 g) as a white solid; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.69 (m, 2H), 1.82 (s, 3H), 2.14 (s, 3H), 2.86 (m, 1H), 3.47 (m, 2H), 4.13 (m, 2H), 7.52 (m, 2H), 7.59 (s, 1H), 7.74 (d, 1H), 7.83 (s, 1H), 7.90 (d, 1H), 8.09 (t, 1H), 8.20 (s, 1H), 8.43 (d, 1H); Mass Spectrum: $M+H^+$ 421.

Example 34

3-[6-[2-(dimethylamino)ethoxy]-4-oxoquinazolin-3(4*H*)-yl]-4-methyl-*N*-(1-methylcyclpropyl)benzamide (AZ12302464)

3-(6-hydroxy-4-oxoquinazolin-3(4*H*)-yl)-4-methyl-*N*-(1-methylcyclpropyl)benzamide (0.200 g), 2-dimethylaminoethyl chloride hydrochloride (0.107 g), potassium carbonate (0.79 g), and sodium iodide (0.01 g) were stirred in acetone (5 ml) at 60°C for 18 hours. The reaction mixture was filtered, the solids washed with acetone, and the filtrate was concentrated. The residue was dissolved in ethyl acetate and washed with 1N NaOH solution, brine, dried (magnesium sulfate) and concentrated under reduced pressure. The residue was triturated with a mixture of ethyl acetate and ether and the resulting solid was filtered and dried under vacuum at 40°C. There was thus obtained the title compound (0.112 g) as a white solid; NMR Spectrum: ($DMSOd_6$) 0.59 (m, 2H), 0.72 (m, 2H), 1.35 (s, 3H), 2.12 (s, 3H), 2.22 (s, 6H), 2.67 (m, 2H), 4.18 (m, 2H), 7.49 (m, 2H), 7.57 (s, 1H), 7.71 (d, 1H), 7.83 (s, 1H), 7.88 (d, 1H), 8.16 (s, 1H), 8.64 (s, 1H); Mass Spectrum $M+H^+$ 421.

The 3-(6-hydroxy-4-oxoquinazolin-3(4*H*)-yl)-4-methyl-*N*-(1-methylcyclpropyl)benzamide used as starting material was prepared as follows:-

A) A stirred mixture of 2-amino-5-methoxybenzoic acid (4 g), trimethylorthoformate (3.93 ml), and acetic acid (0.137 ml) in toluene (100 ml) was heated under reflux for 2 hours. 3-amino-4-methyl-*N*-(1-methylcyclopropyl)benzamide (4.39 g) was added to the reaction mixture and stirring continued in refluxing toluene for 16 hours. The reaction mixture was

allowed to cool and then was diluted with ethyl acetate. The organic solution was then washed with 1N HCl solution, 2N NaOH solution (x 2), brine, dried (magnesium sulfate) and concentrated to a cream coloured solid. The solid was dissolved in ethyl acetate and the insoluble material removed by filtration. *Iso*-hexane was added to the filtrate and concentrated to give 3-(6-methoxy-4-oxoquinazolin-3(4*H*)-yl)-4-methyl-*N*-(1-methylcyclopropylbenzamide (4.3 g); NMR Spectrum: ($DMSOd_6$) 0.59 (m, 2H), 0.72 (m, 2H), 1.35 (s, 3H), 2.12 (s, 3H), 3.89 (s, 3H), 7.50 (m, 2H), 7.56 (m, 1H), 7.72 (d, 1H), 7.83 (s, 1H), 7.88 (d, 1H), 8.17 (s, 1H), 8.63 (s, 1H); Mass Spectrum: $M+Na^+$ 486.

The 3-amino-4-methyl-*N*-(1-methylcyclopropyl)benzamide used as starting material was prepared as follows:-

To a stirred suspension of 4-methyl-3-nitrobenzoic acid (9.06 g) in methylene chloride (50 ml) at 0°C was added oxalyl chloride (8.7 ml) and DMF (1 drop), the reaction was stirred for 3 hours at room temperature. The reaction mixture was concentrated and the residue resuspended in methylene chloride (200 ml), cooled to 0°C and *N,N*-diisopropylethylamine (19.2ml) and (1-methylcyclopropyl)amine hydrochloride (5.95 g) added. The reaction was stirred at room temperature for 18 hours. The reaction was concentrated and the residue resuspended in ethyl acetate (200 ml). The organic layer was washed 2N HCl (2 x 300 ml), saturated aqueous $NaHCO_3$ solution (2 x 200 ml), brine (200 ml), dried (magnesium sulphate) and concentrated to yield the 4-methyl-*N*-(1-methylcyclopropyl)-3-nitrobenzamide as a yellow oil (10.72 g); NMR Spectrum: ($DMSOd_6$) 0.68 (m, 4H), 2.54 (s, 3H), 2.54 (s, 3H), 7.55 (m, 1H), 8.04 (m, 1H), 8.39 (m, 1H), 8.87 (s, 1H); Mass Spectrum: $M+H^+$ 235.

A suspension of 4-methyl-*N*-(1-methylcyclopropyl)-3-nitrobenzamide (10.72 g) and 10% palladium on carbon (300 mg) in ethanol (200 ml) was agitated under a hydrogen atmosphere for 16 hours. The reaction mixture was filtered through diatomaceous earth (Celite®) and the filtrate evaporated to dryness and triturated with *iso*-hexane to give the title compound as a solid (8.32 g); NMR Spectrum: ($DMSOd_6$) 0.64 (m, 4H), 2.08 (s, 3H), 2.08 (s, 3H), 4.91 (s, 2H), 6.91 (m, 2H), 7.04 (d, 1H), 8.27 (s, 1H); Mass Spectrum: $M+H^+$ 205.

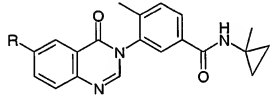
B) To a stirred solution of 3-(6-methoxy-4-oxoquinazolin-3(4*H*)-yl)-4-methyl-*N*-(1-methylcyclopropylbenzamide (3.8 g) in methylene chloride (50 ml) was added 1M boron tribromide in methylene chloride (50 ml) and stirred for 20 hours. The reaction was quenched with water and diluted with 2N NaOH solution until the solid dissolved. The aqueous layer was washed with methylene chloride (2 x), acidified to pH 1 using 2N HCl and extracted with

ethyl acetate (3 x). The combined organic extracts were concentrated and the residue was triturated with a mixture of ethyl acetate and ether and the resulting solid was filtered and dried under vacuum at 40°C. There was thus obtained 3-(6-hydroxy-4-oxoquinazolin-3(4*H*)-yl)-4-methyl-*N*-(1-methylcyclpropyl)benzamide (0.664 g); Mass Spectrum: $M+H^+$ 350.

Example 35

Using an analogous procedure to that described in Example 34, 3-(6-hydroxy-4-oxoquinazolin-3(4*H*)-yl)-4-methyl-*N*-(1-methylcyclpropyl)benzamide was reacted with the appropriate alkyl halide to give the compounds described in Table 15

Table 15



R	Method	Note
2-Piperidin-1-ylethoxy (AZ12304505)	Ex 34	a

Notes

a) The product gave the following data; NMR Spectrum: ($DMSOd_6$) 0.59 (m, 2H), 0.72 (m, 2H), 1.35 (m, 5H), 1.49 (m, 4H), 2.12 (s, 3H), 2.43 (m, 4H), 2.69 (m, 2H), 4.21 (m, 2H), 7.49 (d, 2H), 7.59 (s, 1H), 7.70 (d, 1H), 7.83 (s, 1H), 7.88 (d, 1H), 8.16 (s, 1H), 8.64 (s, 1H); Mass Spectrum: $M+H^+$ 461.

Example 36

***N*-cyclpropyl-3-[(8-[2-(dimethylamino)ethoxy]-4-oxoquinazolin-3(4*H*)-yl)-4-methylbenzamide (AZ12321157)**

Using an analogous procedure to that described in Example 25, *N*-cyclpropyl-3-(8-hydroxy-4-oxoquinazolin-3(4*H*)-yl)-4-methylbenzamide was reacted with 2-dimethylaminoethyl chloride hydrochloride. There was thus obtained the title compound; Mass Spectrum: $M+H^+$ 407

The *N*-cyclopropyl-3-(8-hydroxy-4-oxoquinazolin-3(4*H*)-yl)-4-methylbenzamide used as starting material was prepared as follows :-

A) Using an analogous procedure to that described in paragraph (A) in the portion of Example 24 which is concerned with the preparation of starting material, 2-amino-3-methoxybenzoic acid was reacted with 3-amino-*N*-cyclopropyl-4-methylbenzamide to give *N*-cyclopropyl-3-(8-methoxy-4-oxoquinazolin-3(4*H*)-yl)-4-methylbenzamide (AZ12304507); NMR Spectrum: ($DMSOd_6$) 0.55 (m, 2H), 0.68 (m, 2H), 2.12 (s, 3H), 2.84 (m, 1H), 3.94 (s, 3H), 7.49 (m, 3H), 7.74 (d, 1H), 7.83 (s, 1H), 7.89 (d, 1H), 8.24 (s, 1H), 8.44 (s, 1H); Mass Spectrum: $M+H^+$ 350.

B) Using an analogous procedure to that described in paragraph (B) in the portion of Example 24 which is concerned with the preparation of starting material, *N*-cyclopropyl-3-(8-methoxy-4-oxoquinazolin-3(4*H*)-yl)-4-methylbenzamide was reacted with a 1M solution of boron tribromide in methylene chloride to give *N*-cyclopropyl-3-(8-hydroxy-4-oxoquinazolin-3(4*H*)-yl)-4-methylbenzamide; Mass Spectrum: $M+H^+$ 336.

Example 37

***N*-Cyclopropyl-4-methyl-3-[6-{[(2*S*)-1-methylpyrrolidin-2-yl]methoxy}-4-oxoquinazolin-3(4*H*)-yl]benzamide (AZ12300371)**

N-Cyclopropyl-4-methyl-3-[4-oxo-6-[(2*S*)-pyrrolidin-2-ylmethoxy]quinazolin-3(4*H*)-yl]benzamide (0.15 g) and 38% aqueous formaldehyde (0.284 ml) were stirred in formic acid (3 ml) at 90°C for 16 hours and then concentrated. The residue was partitioned between ethyl acetate and saturated aqueous $NaHCO_3$ solution. The organic layer was washed with brine, dried (magnesium sulfate) and concentrated. Purification by column chromatography on a silica column eluting with 10% methanol/ethyl acetate followed by 10% methanol/ethyl acetate + 1% aqueous ammonia solution to give the title compound (0.12 g) as a white foam solid; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.70 (m, 2H), 1.70 (m, 3H), 1.99 (m, 1H), 2.14 (s, 3H), 2.22 (m, 1H), 2.39 (s, 3H), 2.62 (m, 1H), 2.85 (m, 1H), 2.96 (m, 1H), 3.99 (m, 1H), 4.09 (m, 1H), 7.52 (m, 2H), 7.60 (s, 1H), 7.73 (d, 1H), 7.83 (s, 1H), 7.91 (d, 1H), 8.19 (s, 1H), 8.42 (d, 1H); Mass Spectrum: $M+H^+$ 433.

The *N*-cyclopropyl-4-methyl-3-[4-oxo-6-[(2*S*)-pyrrolidin-2-ylmethoxy]quinazolin-3(4*H*)-yl]benzamide used as starting material was prepared as follows:-

To a solution of *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-fluoro-2-nitrobenzamide (3.0 g) and (*S*)-(-)-1-(*tert*-butoxycarbonyl)-2-pyrrolidinemethanol (2.54 g) in DMF (45 ml) was added sodium hydride (1.34 g of a 60% dispersion in oil) portion-wise (ice bath cooling). The reaction was stirred for 24 hours at room temperature under an atmosphere

of argon. The reaction mixture was then poured into a saturated aqueous ammonium chloride solution (200 ml) and the resulting precipitate was collected by filtration, dissolved in methanol (10 ml) and 4N HCl in dioxane (5 ml) added. The reaction mixture was stirred at room temperature for 16 hours, concentrated and re-precipitated from methanol/ethyl acetate to yield *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-2-nitro-5-[(2*S*)-pyrrolidin-2-ylmethoxy]benzamide hydrochloride salt (2.25 g) as a yellow solid which was used without further purification; Mass Spectrum: $M+H^+$ 439.

N-{5-[(Cyclopropylamino)carbonyl]-2-methylphenyl}-2-nitro-5-[(2*S*)-pyrrolidin-2-ylmethoxy]benzamide hydrochloride salt (2.05 g) and 10% palladium on carbon (0.2 g) were stirred in ethanol (40 ml) and methanol (20 ml) under an atmosphere of hydrogen gas for 19 hours at room temperature. The catalyst was removed by filtration through diatomaceous earth (Celite®) and the filtrate was concentrated. The residue was dissolved in ethanol (40 ml) and stirred with triethylorthoformate (2.16 ml) and glacial acetic acid (0.124 ml) at 80°C for 3 hours and then concentrated. The residue was diluted with ethyl acetate and washed with saturated aqueous $NaHCO_3$ solution, brine, dried (magnesium sulfate) and concentrated. Purification by column chromatography on a silica column eluting with 20% methanol/ethyl acetate followed by 20% methanol/ethyl acetate + 1% aqueous ammonia solution to give *N*-cyclopropyl-4-methyl-3-[4-oxo-6-[(2*S*)-pyrrolidin-2-ylmethoxy]quinazolin-3(4*H*)-yl]benzamide (AZ12299441) (0.837 g) as a cream coloured foam solid; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.70 (m, 2H), 1.49 (m, 1H), 1.61-1.76 (m, 2H), 1.85 (m, 1H), 2.15 (s, 3H), 2.85 (m, 3H), 3.42 (m, 1H), 3.95 (d, 2H), 7.52 (m, 2H), 7.58 (s, 1H), 7.73 (d, 1H), 7.84 (s, 1H), 7.91 (d, 1H), 8.19 (s, 1H), 8.42 (d, 1H); Mass Spectrum: $M+H^+$ 419.

Example 38

***N*-Cyclopropyl-3-[6-{[(2*S*)-1-glycoloylpyrrolidin-2-yl]methoxy}-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide (AZ12312960)**

N-Cyclopropyl-4-methyl-3-[4-oxo-6-[(2*S*)-pyrrolidin-2-ylmethoxy]quinazolin-3(4*H*)-yl]benzamide (0.20 g), triethylamine (0.133 ml), and acetoxyacetyl chloride (0.077 ml) were stirred in methylene chloride (2 ml) under argon at room temperature for 30 minutes. A solution of 2N NaOH (2 ml) and methanol (2 ml) was added to the reaction mixture and stirring continued for 1 hour at room temperature. The reaction mixture was diluted with methylene chloride and washed with brine, dried (magnesium sulfate) and concentrated. Purification by column chromatography on a silica column eluting with 5% methanol/ethyl

acetate to give the title compound (0.113 g) as a white foam solid; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.70 (m, 2H), 1.83-2.10 (m, 4H), 2.14 (s, 3H), 2.86 (m, 1H), 3.40 (m, 2H), 4.05 (m, 3H), 4.25 (m, 1H), 4.32 (m, 1H), 4.52 (t, 1H), 7.53 (m, 2H), 7.60 (s, 1H), 7.74 (d, 1H), 7.84 (s, 1H), 7.91 (d, 1H), 8.19 (s, 1H), 8.43 (d, 1H); Mass Spectrum: $M+H^+$ 477.

Example 39

***N*-Cyclopropyl-4-methyl-3-[6-{[(2*R*)-1-methylpyrrolidin-2-yl]methoxy}-4-oxoquinazolin-3(4*H*)-yl]benzamide (AZ12304522)**

N-Cyclopropyl-4-methyl-3-[4-oxo-6-[(2*R*)-pyrrolidin-2-ylmethoxy]quinazolin-3(4*H*)-yl]benzamide (0.15 g) and 38% aqueous formaldehyde (0.284 ml) were stirred in formic acid (3 ml) at 90°C for 4 hours and then concentrated. The residue was partitioned between ethyl acetate and saturated aqueous $NaHCO_3$ solution. The organic layer was washed with brine, dried (magnesium sulfate) and concentrated. Purification by column chromatography on a silica column eluting with 10% methanol/ethyl acetate followed by 10% methanol/ethyl acetate + 1% aqueous ammonia solution to give the title compound (0.128 g) as a pale yellow foam solid; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.70 (m, 2H), 1.70 (m, 3H), 1.99 (m, 1H), 2.14 (s, 3H), 2.21 (m, 1H), 2.40 (s, 3H), 2.61 (m, 1H), 2.85 (m, 1H), 2.96 (m, 1H), 3.99 (m, 1H), 4.10 (m, 1H), 7.52 (m, 2H), 7.60 (s, 1H), 7.73 (d, 1H), 7.85 (s, 1H), 7.91 (d, 1H), 8.20 (s, 1H), 8.43 (d, 1H); Mass Spectrum: $M+H^+$ 433.

The *N*-cyclopropyl-4-methyl-3-[4-oxo-6-[(2*R*)-pyrrolidin-2-ylmethoxy]quinazolin-3(4*H*)-yl]benzamide used as starting material was prepared as follows:-

To a solution of *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-5-fluoro-2-nitrobenzamide (3.0 g) and (*R*)-(+)-1-(*tert*-butoxycarbonyl)-2-pyrrolidinemethanol (2.54 g) in DMF (45 ml) was added sodium hydride (1.54 g of a 60% dispersion in oil) portion-wise (ice bath cooling). The reaction was stirred for 43 hours at room temperature under an atmosphere of argon. The reaction mixture was then poured into a saturated aqueous ammonium chloride solution (200 ml) and the resulting precipitate was collected by filtration, dissolved in methanol (10 ml) and 4N HCl in dioxane (5 ml) added. The reaction mixture was stirred at room temperature for 16 hours, concentrated and re-precipitated from methanol/ethyl acetate to yield *N*-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-2-nitro-5-[(2*R*)-pyrrolidin-2-ylmethoxy]benzamide hydrochloride salt (3.32 g) as a yellow solid; NMR Spectrum: ($DMSOd_6$) 0.64 (m, 2H), 0.75 (m, 2H), 1.83 (m, 1H), 1.95-2.12 (m, 2H), 2.21 (m, 1H), 2.37

(s, 3H), 2.91 (m, 1H), 3.30 (m, 2H), 4.02 (m, 1H), 4.45 (m, 1H), 4.55 (m, 1H), 7.37 (m, 3H), 7.70 (d, 1H), 8.02 (s, 1H), 8.29 (d, 1H), 8.49 (d, 1H), 9.50 (s, 1H), 10.22 (s, 1H); Mass Spectrum: $M+H^+$ 439.

N-{5-[(Cyclopropylamino)carbonyl]-2-methylphenyl}-2-nitro-5-[(2*R*)-pyrrolidin-2-ylmethoxy]benzamide hydrochloride salt (3.32 g) and 10% Palladium on carbon (0.332 g) were stirred in ethanol (65 ml) and methanol (40 ml) under an atmosphere of hydrogen gas for 2 hours at room temperature. The catalyst was removed by filtration through diatomaceous earth (Celite®) and the filtrate was concentrated under reduced pressure. The residue was dissolved in ethanol (65 ml) and stirred with triethylorthoformate (3.14 ml) and glacial acetic acid (0.18 ml) at 80°C for 1.5 hours and then concentrated. The residue was diluted with ethyl acetate and washed with saturated aqueous $NaHCO_3$ solution, brine, dried (magnesium sulfate) and concentrated. Purification by column chromatography on a silica column eluting with 20% methanol/ethyl acetate followed by 20% methanol/ethyl acetate + 1% aqueous ammonia solution to give *N*-cyclopropyl-4-methyl-3-[4-oxo-6-[(2*R*)-pyrrolidin-2-ylmethoxy]quinazolin-3(4*H*)-yl]benzamide (AZ12304521) (0.763 g) as a yellow/brown foam solid; NMR Spectrum: ($DMSOd_6$) 0.57 (m, 2H), 0.70 (m, 2H), 1.49 (m, 1H), 1.68 (m, 2H), 1.86 (m, 1H), 2.14 (s, 3H), 2.85 (m, 3H), 3.44 (m, 1H), 3.94 (d, 2H), 7.53 (m, 2H), 7.59 (s, 1H), 7.72 (d, 1H), 7.83 (s, 1H), 7.91 (d, 1H), 8.19 (s, 1H), 8.44 (d, 1H); Mass Spectrum: $M+H^+$ 419.

Example 40

N-Cyclopropyl-4-methyl-3-[6-(1-methylpiperidin-4-yl)-4-oxoquinazolin-3(4*H*)-yl]benzamide (AZ12287327)

N-Cyclopropyl-4-methyl-3-[6-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-4-oxoquinazolin-3(4*H*)-yl]benzamide (0.284 g) and 10% Palladium on carbon (0.028 g) were stirred in ethanol (6 ml) and acetic acid (0.5 ml) under an atmosphere of hydrogen for 24 hours. The catalyst was removed by filtration through diatomaceous earth (Celite®) and the filtrate was concentrated under reduced pressure. Purification by column chromatography on a silica column eluting with 10% methanol/ethyl acetate + 1% aqueous ammonia solution to give the title compound (0.140 g) as a white foam solid; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.69 (m, 2H), 1.78 (m, 4H), 2.00 (m, 2H), 2.13 (s, 3H), 2.20 (s, 3H), 2.67 (m, 1H), 2.88 (m, 3H), 7.52 (d, 1H), 7.71 (d, 1H), 7.82 (m, 2H), 7.90 (d, 1H), 8.02 (s, 1H), 8.24 (s, 1H), 8.42 (d, 1H); Mass Spectrum: $M+H^+$ 417.

The *N*-cyclopropyl-4-methyl-3-[6-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-4-oxoquinazolin-3(4*H*)-yl]benzamide used as starting material was prepared as follows:-

A stirred mixture of 2-amino-5-iodobenzoic acid (1.0 g), trimethyl orthoformate (0.83 ml), and acetic acid (0.022 ml) in toluene (15 ml) was heated under reflux for 2 hours. 3-Amino-*N*-cyclopropyl-4-methylbenzamide (0.65 g) was added to the reaction mixture and stirred at reflux for 16 hours. The reaction mixture was allowed to cool and diluted with ethyl acetate. The organic solution was then washed with 1N HCl solution, 2N NaOH solution (x 2), brine, dried (magnesium sulfate), and concentrated to give *N*-cyclopropyl-3-(6-iodo-4-oxoquinazolin-3(4*H*)-yl)-4-methylbenzamide (AZ12233711) (1.22 g) as an off white solid; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.70 (m, 2H), 2.14 (s, 3H), 2.85 (m, 1H), 7.52 (d, 1H), 7.58 (d, 1H), 7.88 (s, 1H), 7.92 (d, 1H), 8.20 (d, 1H), 8.34 (s, 1H), 8.42 (d, 1H), 8.49 (s, 1H); Mass Spectrum: $M+H^+$ 446.

To a nitrogen flushed flask containing *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (1.04 g), potassium carbonate (0.869 g), and 1,1'-bis(diphenylphosphino)ferrocene-palladium (II) dichloride (0.11 g) was added a solution of *N*-cyclopropyl-3-(6-iodo-4-oxoquinazolin-3(4*H*)-yl)-4-methylbenzamide (1.0 g) in DMF (14 ml). The reaction mixture was stirred for 16 hours at 80°C. The reaction mixture was diluted with ethyl acetate and washed with water (5 x), brine, dried (magnesium sulfate) and concentrated. The resulting solid was dissolved in 4N HCl in dioxane (5 ml) and methanol (5 ml) and stirred at room temperature for 2 hours. The precipitate was collected by filtration and washed with ethyl acetate and diethyl ether. Purification by column chromatography on a silica column eluting with 10% methanol/ethyl acetate followed by 20% methanol/ethyl acetate + 1% aqueous ammonia solution gave *N*-cyclopropyl-4-methyl-3-[4-oxo-6-(1,2,3,6-tetrahydropyridin-4-yl)quinazolin-3(4*H*)-yl]benzamide (AZ12267331) (0.393 g) as a light brown solid; NMR Spectrum: ($DMSOd_6$) 0.54 (m, 2H), 0.69 (m, 2H), 2.15 (s, 3H), 2.43 (m, 2H), 2.85 (m, 1H), 2.94 (t, 2H), 3.40 (s, 2H), 6.45 (s, 1H), 7.53 (d, 1H), 7.74 (d, 1H), 7.86 (s, 1H), 7.90 (d, 1H), 8.05 (d, 1H), 8.12 (s, 1H), 8.29 (s, 1H), 8.49 (d, 1H); Mass Spectrum: $M+H^+$ 401.

N-Cyclopropyl-4-methyl-3-[4-oxo-6-(1,2,3,6-tetrahydropyridin-4-yl)quinazolin-3(4*H*)-yl]benzamide (0.293 g) and 38% aqueous formaldehyde (0.577 ml) were stirred in formic acid (6 ml) at 90°C for 3.5 hours and then concentrated. The residue was partitioned between ethyl acetate and saturated aqueous $NaHCO_3$ solution. The organic layer was washed with brine,

dried (magnesium sulfate) and concentrated. Purification by column chromatography on a silica column eluting with 10% methanol/ethyl acetate followed by 10% methanol/ethyl acetate + 1% aqueous ammonia solution to give *N*-cyclopropyl-4-methyl-3-[6-(1-methyl-1,2,3,6-tetrahydropyridin–4-yl)-4-oxoquinazolin-3(4*H*)-yl]benzamide (AZ12285777) (0.257 g) as a white foam solid; NMR Spectrum: ($DMSOd_6$) 0.55 (m, 2H), 0.70 (m, 2H), 2.15 (s, 3H), 2.30 (s, 3H), 2.59 (m, 4H), 2.85 (m, 1H), 3.08 (s, 2H), 6.40 (s, 1H), 7.52 (d, 1H), 7.74 (d, 1H), 7.85 (s, 1H), 7.91 (d, 1H), 8.06 (d, 1H), 8.14 (s, 1H), 8.29 (s, 1H), 8.43 (d, 1H); Mass Spectrum: $M+H^+$ 415.

tert-Butyl 4-{[(trifluoromethyl)sulfonyl]oxy}-3,6-dihydropyridine-1(2H)-carboxylate (124 g), bis(pinacolato)diboron (106.7 g), potassium acetate (110.3 g), (diphenylphosphine)ferrocene (6.27 g) and bis[(diphenylphosphine)ferrocene]dichloro palladium (II) (8.37 g) were suspended in dioxane (1.8 l) and stirred at 80°C for 18 hours. Reaction mixture was cooled to room temperature and concentrated. Ethyl acetate was added, washed with water, dried (magnesium sulphate) and concentrated. Purification by column chromatography on a silica column eluting with 10% ethyl acetate/*iso*-hexane to give *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate as a white solid (93 g); NMR Spectrum: 1.21 (s, 12H), 1.40 (s, 9H), 2.08 (t, 2H), 3.33 (m, 2H), 3.87 (s, 2H), 6.39 (s, 1H); Mass Spectrum: $M+H^+$ 310.

To a stirred 1M solution of lithium bis(trimethylsilyl)amide in THF (140 ml) at –78°C was added dropwise over 10 minutes a solution of *tert*-butyl 4-oxopiperidine-1-carboxylate (27.9 g) in THF (100 ml). The solution was stirred at –78°C for a further 30 minutes when *N*-phenyltrifluoromethanesulfonimide (50 g) was added over 30 minutes. The resultant solution was warmed to room temperature and stirred for 18 hours. The solution was washed with 2N NaOH and the aqueous layers extracted with diethyl ether. The organic layers were combined, dried (sodium sulphate) and concentrated to yield the title compound as an oil (41 g). NMR Spectrum: ($CDCl_3$) 1.45 (s, 9H), 2.43 (m, 2H), 3.63 (t, 2H), 4.05 (d, 2H), 5.77 (m, 1H); Mass Spectrum: $M+H^+$ 332.

Example 41

***N*-Cyclopropyl-3-[6-[3-(dimethylamino)propyl]-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide (AZ12285776)**

N-Cyclopropyl-3-[6-[3-(dimethylamino)prop-1-yn-1-yl]-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide (0.097 g) and 10% Palladium on carbon (0.01 g) were stirred in ethanol (2

ml) and methanol (0.5 ml) under an atmosphere of hydrogen for 2 hours. The catalyst was removed by filtration through diatomaceous earth (Celite®) and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on a silica column eluting with 10% methanol/ethyl acetate followed by 10% methanol/ethyl acetate + 1% aqueous ammonia solution to give the title compound (0.068 g) as a white foam solid; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.70 (m, 2H), 1.78 (m, 2H), 2.15 (s, 9H), 2.23 (t, 2H), 2.78 (t, 2H), 2.86 (m, 1H), 7.53 (d, 1H), 7.71 (d, 1H), 7.78 (d, 1H), 7.83 (s, 1H), 7.91 (d, 1H), 8.02 (s, 1H), 8.25 (s, 1H), 8.42 (d, 1H); Mass Spectrum: $M+H^+$ 405.

The *N*-cyclopropyl-3-[6-[3-(dimethylamino)prop-1-yn-1-yl]-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide used as starting material was prepared as follows:-

A mixture of *N*-cyclopropyl-3-(6-iodo-4-oxoquinazolin-3(4*H*)-yl)-4-methylbenzamide (0.213 g), dichlorobis(triphenylphosphine) palladium (0.0084 g), copper iodide (0.0046 g), and triethylamine (0.334 ml) was stirred in acetonitrile (3 ml) and dimethyl formamide (0.1 ml) under argon for 20 minutes. 1-Dimethylamino-2-propyne (0.052 ml) in acetonitrile (2 ml) was added dropwise and the reaction mixture was stirred for 24 hours at room temperature. The residue obtained after removal of acetonitrile was dissolved in ethyl acetate and washed with water (2 x), brine, dried (magnesium sulfate) and concentrated. Purification by column chromatography on an ion exchange column (isolute SCX-2 column from International Sorbent Technology Limited, Henoed, Mid-Glamorgan, UK) washing with methanol initially and then eluting with a 99:1 mixture of methanol and aqueous ammonia solution gave, after re-precipitation from methanol/ethyl acetate/ether, *N*-cyclopropyl-3-[6-[3-(dimethylamino)prop-1-yn-1-yl]-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide (AZ12285770) (0.111 g) as a fawn solid; NMR Spectrum: ($DMSOd_6$) 0.55 (m, 2H), 0.69 (m, 2H), 2.15 (s, 3H), 2.29 (s, 6H), 2.85 (m, 1H), 3.52 (s, 2H), 7.51 (d, 1H), 7.78 (d, 1H), 7.87 (s, 1H), 7.91 (m, 2H), 8.18 (s, 1H), 8.35 (s, 1H), 8.43 (d, 1H); Mass Spectrum: $M+H^+$ 401.

Example 42

Methyl(2*E*)-3-(3-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4-oxo-3,4-dihydroquinazolin-6-yl)acrylate (AZ12285742)

Palladium acetate (0.02 g) and triphenylphosphine (0.038 g) was added to a stirred mixture *N*-cyclopropyl-3-(6-iodo-4-oxoquinazolin-3(4*H*)-yl)-4-methylbenzamide (0.20 g), methyl acrylate (0.4 ml) and triethylamine (0.63 ml) in anhydrous tetrahydrofuran (15 ml) under an argon atmosphere. The mixture was heated to 60°C and stirred for 2 hours. The

reaction mixture was evaporated, dissolved in ethyl acetate (100 ml) and washed with water (100 ml) and brine (100 ml). The organic phase was dried (magnesium sulphate) and evaporated and the residue purified by column chromatography on a silica column using initially *iso*-hexane and then a 1:1 mixture of *iso*-hexane and ethyl acetate as eluent. There was thus obtained the title compound (0.14 g); NMR Spectrum: ($DMSOd_6$) 0.57 (m, 2H), 0.70 (m, 2H), 2.17 (s, 3H), 2.86 (m, 1H), 3.76 (s, 3H), 6.80 (d, 1H), 7.55 (m, 2H), 7.63 (m, 1H), 7.86 (m, 2H), 8.31 (m, 1H), 8.37 (s, 1H), 8.45 (m, 2H); Mass Spectrum: $M+H^+$ 404.

Example 43

***N*-cyclopropyl-4-methyl-3-(4-oxoquinazolin-3(4H)-yl)benzamide (AZ12228137)**

Triethylorthoformate (0.15 ml) was added to a stirred mixture of 3-[(2-aminobenzoyl)amino]-*N*-cyclopropyl-4-methylbenzamide (0.093 g) and glacial acetic acid (0.017 ml) in ethanol (10 ml). The mixture was heated to 80°C and stirred for 16 hours. The reaction mixture was evaporated, dissolved in ethyl acetate (50 ml) and washed with a saturated $NaHCO_3$ solution (100 ml). The organic phase was dried over magnesium sulphate, filtered then concentrated *in vacuo* onto silica gel (0.1 g). The residue was purified by column chromatography (isolute silica 20g column from International Sorbent Technology Limited, Henoed, Mid-Glamorgan, UK) using a gradient of 10% *iso*-propanol/*iso*-hexane through to 50% *iso*-propanol/*iso*-hexane to give the title compound as a white solid (0.062 g); NMR Spectrum: ($DMSOd_6$) 0.55 (m, 2H), 0.68 (m, 2H), 2.14 (s, 3H), 2.84 (m, 1H), 7.52 (d, 1H), 7.62 (t, 1H), 7.78 (d, 1H), 7.84 (d, 1H), 7.89 (m, 2H), 8.21 (m, 1H), 8.30 (s, 1H), 8.41 (d, 1H); Mass Spectrum: $M+H^+$ 320.

The 3-[(2-aminobenzoyl)amino]-*N*-cyclopropyl-4-methylbenzamide used as starting material was prepared as follows :-

To a stirred solution of 2-nitrobenzoic acid (0.903 g) in anhydrous methylene chloride (20 ml) at room temperature was added oxalyl chloride (0.52 ml). The mixture was stirred for 2 hours and then concentrated. The residue was dissolved in methylene chloride (20 ml), *N,N*-diisopropylethylamine (2.82 ml) and 3-Amino-*N*-cyclopropyl-4-methylbenzamide (1.03 g) were added and the reaction stirred for 2 hours and then concentrated. The residue was portioned between ethyl acetate (200 ml) and 2N HCl (150 ml). The ethyl acetate layer was washed with 1N NaOH solution (100 ml), water/brine (150 ml), dried (magnesium sulfate) and concentrated to give *N*-cyclopropyl-4-methyl-3-[(2-nitrobenzoyl)amino]benzamide as a yellow solid (1.52 g); NMR Spectrum: ($DMSOd_6$) 0.55 (m, 2H), 0.68 (m, 2H), 2.30 (s, 3H),

2.85 (m, 1H), 7.31 (d, 1H), 7.61 (m, 1H), 7.72 to 7.88 (m, 3H), 7.89 (d, 1H), 8.13 (m, 1H), 8.40 (d, 1H), 10.21 (s, 1H); Mass Spectrum: $M+H^+$ 340.

Nickel acetate tetrahydrate (0.119 g) was added to a suspension of Borohydride on Amerlite IRA-400 resin (8.96 g) in methanol (90 ml). Gas was evolved and the resin turned from a light gold to black. After 1 minute the *N*-cyclopropyl-4-methyl-3-[(2-nitrobenzoyl)amino]benzamide (1.52 g) was added in a single portion and the mixture stirred at room temperature. After 1 hour the reaction was filtered through diatomaceous earth (Celite®) and the filtrate concentrated onto silica gel (2.0 g). Purification by column chromatography (isolute silica 50g column from International Sorbent Technology Limited, Henoed, Mid-Glamorgan, UK) using a gradient of 0% *iso*-propanol/*iso*-hexane through to 50% *iso*-propanol/*iso*-hexane to give 3-[(2-aminobenzoyl)amino]-*N*-cyclopropyl-4-methylbenzamide as a white solid (0.159 g); NMR Spectrum: ($DMSOd_6$) 0.58 (m, 2H), 0.69 (m, 2H), 2.26 (s, 3H), 2.85 (m, 1H), 6.40 (s, 2H), 6.59 (t, 1H), 6.76 (d, 1H), 7.21 (t, 1H), 7.33 (d, 1H), 7.63 (m, 1H), 7.72 (d, 1H), 7.78 (d, 1H), 8.36 (d, 1H), 9.70 (d, 1H); Mass Spectrum: $M+H^+$ 310.

Example 44

N-cyclopropyl-3-[6-{[2-(dimethylamino)ethyl]sulfonyl}-4-oxoquinazoline-3(4*H*)-yl]-4-methylbenzamide (AZ12319268)

p-Toluene sulfonylimidizole (0.264 mg) was added to a stirred mixture of *N*-cyclopropyl-4-methyl-3-(4-oxo-6-thiomorphin-4-ylquinazoline-3(4*H*)-yl)benzamide (0.2 g), hydrogen peroxide (30%solution in water) (2.38 ml) and 2N NaOH (0.595 ml) in methanol (10 ml). The mixture was stirred for 16 hours at room temperature. The reaction was acidified with 1N HCl and purified by column chromatography on an ion exchange column (isolute SCX column from International Sorbent Technology Limited, Henoed, Mid-Glamorgan, UK) using initially methanol and then a 99:1 mixture of methanol and aqueous ammonia solution. Fractions containing product were combined and evaporated and the residue was dissolved in methylene chloride and washed with water. The organic extracts were combined, dried (magnesium sulphate), concentrated and the residue was triturated with ethyl acetate and methylene chloride. The resultant solid was filtered and dried under vacuum at 40°C. There was thus obtained the title compound; NMR Spectrum: ($DMSOd_6$) 0.55 (m, 2H), 0.69 (m, 2H), 2.17 (s, 3H), 2.48 (s, 6H), 2.84 (m, 1H), 4.05 (m, 2H), 4.34 (m, 2H), 7.52 (m, 2H), 7.90 (m, 3H), 8.23 (d, 1H), 8.45 (m, 2H); Mass Spectrum: $M+Na^+$ 478.

Example 45

***N*-Cyclopropyl-3-[6-(4-isopropylpiperazin-1-yl)-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide hydrochloride salt**

To a stirred solution of *N*-cyclopropyl-3-[6-(4-isopropylpiperazin-1-yl)-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide (0.010 g) in ethyl acetate (0.5 ml) was added a 4N HCl in dioxane (0.0056 ml) at room temperature. The mixture was stirred at room temperature for a further 30 minutes. The reaction mixture was evaporated to give the title compound; NMR Spectrum: ($DMSOd_6$) 0.55 (m, 2H), 0.70 (m, 2H), 1.24 (m, 6H), 2.13 (s, 3H), 2.85 (m, 1H), 3.00-3.50 (m, 9H), 7.53 (m, 2H), 7.69 (m, 2H), 7.84 (s, 1H), 7.91 (d, 1H), 8.12 (s, 1H), 8.46 (d, 1H), 10.80 (br s, 1H).

Example 46

***N*-Cyclopropyl-4-methyl-3-[6-(4-methylpiperazin-1-yl)-4-oxoquinazolin-3(4H)-yl]benzamide hydrochloride salt**

Using an analogous procedure to that described in Example 45, 4N HCl in dioxane was reacted with *N*-cyclopropyl-4-methyl-3-[6-(4-methylpiperazin-1-yl)-4-oxoquinazolin-3(4H)-yl]benzamide to gave the title compound; NMR Spectrum: ($DMSOd_6$) 0.57 (m, 2H), 0.70 (m, 2H), 2.14 (s, 3H), 2.82 (d, 3H), 2.87 (m, 1H), 3.22 (m, 4H), 3.52 (d, 2H), 4.01 (m, 2H), 7.53 (d, 1H), 7.58 (d, 1H), 7.70 (m, 2H), 7.85 (s, 1H), 7.92 (m, 1H), 8.17 (s, 1H), 8.48 (d, 1H), 11.05 (s, 1H).

Example 47

***N*-Cyclopropyl-3-[6-{[(3*S*)-1-isopropylpyrrolidin-3-yl]oxy}-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide hydrochloride salt**

Using an analogous procedure to that described in Example 45, 4N HCl in dioxane was reacted with *N*-cyclopropyl-3-[6-{[(3*S*)-1-isopropylpyrrolidin-3-yl]oxy}-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide to gave the title compound; NMR Spectrum: ($DMSOd_6$) 0.55 (m, 2H), 0.70 (m, 2H), 1.30 (m, 6H), 2.13 (s, 3H), 2.24 (m, 1H), 2.86 (m, 1H), 3.28-3.70 (m, 6H), 5.38 (m, 1H), 7.55 (m, 2H), 7.64 (s, 1H), 7.78 (d, 1H), 7.84 (s, 1H), 7.93 (d, 1H), 8.22 (s, 1H), 8.48 (m, 1H), 11.76 (br s, 0.5H), 11.40 (br s, 0.5H).

Example 48

***N*-Cyclopropyl-3-[6-{[2-(dimethylamino)ethyl]thio}-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide hydrochloride salt**

Using an analogous procedure to that described in Example 45, 4N HCl in dioxane was reacted with *N*-cyclopropyl-3-[6-{[2-(dimethylamino)ethyl]thio}-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide to gave the title compound; NMR Spectrum: ($DMSOd_6$) 0.58 (m, 2H), 0.70 (m, 2H), 2.15 (s, 3H), 2.70 (s, 6H), 2.85 (m, 1H), 3.14 (t, 2H), 3.45 (m, 2H), 7.53 (d, 1H), 7.78 (d, 1H), 7.85 (s, 1H), 7.91 (d, 1H), 7.95 (d, 1H), 8.12 (s, 1H), 8.31 (s, 1H), 8.50 (d, 1H), 10.65 (br s, 1H)

Example 49

***N*-Cyclopropyl-3-[6-[3-(dimethylamino)propyl]-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide hydrochloride salt**

Using an analogous procedure to that described in Example 45, 4N HCl in dioxane was reacted with *N*-cyclopropyl-3-[6-[3-(dimethylamino)propyl]-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide to gave the title compound; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.70 (m, 2H), 2.00 (m, 2H), 2.13 (s, 3H), 2.60 (s, 6H), 2.80-2.93 (m, 5H), 7.53 (d, 1H), 7.73 (d, 1H), 7.80 (d, 1H), 7.85 (s, 1H), 7.91 (d, 1H), 8.08 (s, 1H), 8.29 (s, 1H), 8.48 (d, 1H)

Example 50

***N*-Cyclopropyl-4-methyl-3-[4-oxo-6-(2-piperidin-1-ylethoxy)quinazolin-3(4*H*)-yl]benzamide hydrochloride salt**

Using an analogous procedure to that described in Example 45, 4N HCl in dioxane was reacted with *N*-cyclopropyl-3-[6-[3-(dimethylamino)propyl]-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide to gave the title compound; NMR Spectrum: ($DMSOd_6$) 0.57 (m, 2H), 0.70 (m, 2H), 1.40 (m, 1H), 1.70 (m, 1H), 1.80 (m, 4H), 2.14 (s, 3H), 2.86 (m, 1H), 3.02 (m, 2H), 3.52 (m, 4H), 4.60 (m, 2H), 7.53 (d, 1H), 7.59 (d, 1H), 7.65 (s, 1H), 7.79 (d, 1H), 7.86 (s, 1H), 7.92 (d, 1H), 8.24 (s, 1H), 8.49 (d, 1H), 10.69 (br s, 1H).

Example 51

***N*-Cyclopropyl-3-[6-(4-isopropylpiperazin-1-yl)-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide methanesulfonate salt**

Using an analogous procedure to that described in Example 45, 1N methanesulfonic acid in ethyl acetate was reacted with *N*-cyclopropyl-3-[6-(4-isopropylpiperazin-1-yl)-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide to gave the title compound; NMR Spectrum:

($DMSOd_6$) 0.56 (m, 2H), 0.70 (m, 2H), 1.30 (d, 6H), 2.14 (s, 3H), 2.35 (s, 3H), 2.85 (m, 1H), 3.10-3.28 (m, 4H), 3.55 (m, 3H), 4.07 (m, 2H), 7.53 (d, 1H), 7.57 (s, 1H), 7.71 (m, 2H), 7.82 (s, 1H), 7.91 (d, 1H), 8.18 (s, 1H), 8.44 (d, 1H), 9.40 (br s, 1H).

Example 52

_N_-Cyclopropyl-3-[6-{[(3*S*)-1-isopropylpyrrolidin-3-yl]oxy}-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide methanesulfonate salt

Using an analogous procedure to that described in Example 45, 1N methanesulfonic acid in ethyl acetate was reacted with *N*-cyclopropyl-3-[6-{[(3*S*)-1-isopropylpyrrolidin-3-yl]oxy}-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide to gave the title compound; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.70 (m, 2H), 1.30 (m, 6H), 2.14 (s, 3H), 2.26 (m, 1H), 2.36 (s, 3H), 2.85 (m, 1H), 3.27-4.00 (m, 6H), 5.38 (m, 1H), 7.54 (d, 1H), 7.58 (d, 1H), 7.63 (s, 1H), 7.80 (d, 1H), 7.84 (s, 1H), 7.91 (d, 1H), 8.23 (s, 1H), 8.45 (m, 1H), 9.95 (br d, 1H).

Example 53

_N_-Cyclopropyl-3-[6-{[2-(dimethylamino)ethyl]thio}-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide methanesulfonate salt

Using an analogous procedure to that described in Example 45, 1N methanesulfonic acid in ethyl acetate was reacted with *N*-cyclopropyl-3-[6-{[2-(dimethylamino)ethyl]thio}-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide to gave the title compound; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.70 (m, 2H), 2.15 (s, 3H), 2.33 (s, 3H), 2.85 (m, 7H), 3.32 (m, 2H), 3.45 (m, 2H), 7.53 (d, 1H), 7.79 (d, 1H), 7.83 (s, 1H), 7.90-7.97 (m, 2H), 8.17 (s, 1H), 8.32 (s, 1H), 8.47 (d, 1H), 9.50 (br s, 1H).

Example 54

_N_-Cyclopropyl-3-[6-[3-(dimethylamino)propyl]-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide methanesulfonate salt

Using an analogous procedure to that described in Example 45, 1N methanesulfonic acid in ethyl acetate was reacted with *N*-cyclopropyl-3-[6-[3-(dimethylamino)propyl]-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide to gave the title compound; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.70 (m, 2H), 2.01 (m, 2H), 2.14 (s, 3H), 2.33 (s, 3H), 2.80 (s, 6H), 2.83 (m, 3H), 3.10 (m, 2H), 7.53 (d, 1H), 7.74 (d, 1H), 7.82 (m, 2H), 7.91 (d, 1H), 8.10 (s, 1H), 8.29 (s, 1H), 8.45 (d, 1H), 9.31 (br s, 1H).

Example 55

***N*-Cyclopropyl-4-methyl-3-[4-oxo-6-(2-piperidin-1-ylethoxy)quinazolin-3(4*H*)-yl]benzamide methanesulfonate**

Using an analogous procedure to that described in Example 45, 1N methanesulfonic acid in ethyl acetate was reacted with *N*-cyclopropyl-4-methyl-3-[4-oxo-6-(2-piperidin-1-ylethoxy)quinazolin-3(4*H*)-yl]benzamide to gave the title compound; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.70 (m, 2H), 1.40 (m, 1H), 1.70 (m, 3H), 1.83 (m, 2H), 2.14 (s, 3H), 2.35 (s, 3H), 2.85 (m, 1H), 3.02 (m, 2H), 3.54 (m, 4H), 4.51 (m, 2H), 7.53 (d, 1H), 7.59 (d, 1H), 7.69 (s, 1H), 7.79 (d, 1H), 7.83 (s, 1H), 7.91 (d, 1H), 8.23 (s, 1H), 8.45 (d, 1H), 9.33 (br s, 1H).

Example 56

***N*-Cyclopropyl-3-[6-(4-isopropylpiperazin-1-yl)-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide bismethanesulfonate salt**

Using an analogous procedure to that described in Example 45, two equivalents of 1N methanesulfonic acid in ethyl acetate was reacted with *N*-cyclopropyl-3-[6-(4-isopropylpiperazin-1-yl)-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide to gave the title compound; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.70 (m, 2H), 1.15 (m, 6H), 1.92 (s, 1H), 2.14 (s, 3H), 2.32 (s, 6H), 2.54 (m, 4H), 2.87 (m, 1H), 2.99 (m, 1H), 3.18 (m, 4H), 4.06 (m, 1H), 7.52 (m, 2H), 7.67 (s, 2H), 7.82 (d, 1H), 7.91 (m, 1H), 8.11 (s, 1H), 8.44 (d, 1H).

Example 57

***N*-Cyclopropyl-4-methyl-3-[6-(4-methylpiperazin-1-yl)-4-oxoquinazolin-3(4H)-yl]benzamide bismethanesulfonate salt**

Using an analogous procedure to that described in Example 45, two equivalents of 1N methanesulfonic acid in ethyl acetate was reacted with *N*-cyclopropyl-4-methyl-3-[6-(4-methylpiperazin-1-yl)-4-oxoquinazolin-3(4H)-yl]benzamide to gave the title compound; NMR Spectrum: ($DMSOd_6$) 0.56 (m, 2H), 0.70 (m, 2H), 2.13 (s, 1H), 2.40 (s, 6H), 2.87 (m, 1H), 2.89 (d, 3H), 3.10 - 3.30 (m, 4H), 3.58 (m, 2H), 4.05 (m, 2H), 7.52 (d, 1H), 7.59 (d, 1H), 7.71 (m, 2H), 7.84 (s, 1H), 7.91 (m, 1H), 8.22 (s, 1H), 8.47 (d, 1H), 9.74 (s, 1H).

Example 58

***N*-Cyclopropyl-3-[6-{[(3*S*)-1-isopropylpyrrolidin-3-yl]oxy}-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide bismethanesulfonate salt**

Using an analogous procedure to that described in Example 45, two equivalents of 1N methanesulfonic acid in ethyl acetate was reacted with *N*-cyclopropyl-3-[6-{[(3*S*)-1-isopropylpyrrolidin-3-yl]oxy}-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide to gave the title compound; NMR Spectrum: ($DMSOd_6$) 0.62 (m, 2H), 0.76 (m, 2H), 1.36 (m, 6H), 2.20 (s, 3H), 2.47 (s, 6H), 2.91 (m, 3H), 3.33 - 4.01 (m, 6H), 5.44 (m, 1H), 7.58 - 7.66 (m, 2H), 7.70 (d, 1H), 7.85 (d, 1H), 7.90 (m, 1H), 7.97 (m, 1H), 8.32 (s, 1H), 8.51 (d, 1H), 10.05 (m, 1H).

Example 59

***N*-Cyclopropyl-3-[6-{[2-(dimethylamino)ethyl]thio}-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide bismethanesulfonate salt**

Using an analogous procedure to that described in Example 45, two equivalents of 1N methanesulfonic acid in ethyl acetate was reacted with *N*-cyclopropyl-3-[6-{[2-(dimethylamino)ethyl]thio}-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide to gave the title compound; NMR Spectrum: ($DMSOd_6$) 0.62 (m, 2H), 0.76 (m, 2H), 2.21 (s, 3H), 2.47 (s, 6H), 2.89 (d, 6H), 2.93 (m, 1H), 3.37 (m, 2H), 3.52 (m, 2H), 7.60 (d, 1H), 7.84 (d, 1H), 7.90 (d, 1H), 7.99 (m, 2H), 8.20 (d, 1H), 8.40 (s, 1H), 8.52 (d, 1H), 9.58 (s, 1H).

Example 60

***N*-Cyclopropyl-3-[6-[3-(dimethylamino)propyl]-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide bismethanesulfonate salt**

Using an analogous procedure to that described in Example 45, two equivalents of 1N methanesulfonic acid in ethyl acetate was reacted with *N*-cyclopropyl-3-[6-[3-(dimethylamino)propyl]-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide to gave the title compound; NMR Spectrum: ($DMSOd_6$) 0.57 (m, 2H), 0.70 (m, 2H), 1.91 (s, 2H), 2.15 (s, 3H), 2.40 (s, 6H), 2.80 (d, 6H), 2.82 - 2.90 (m, 3H), 3.10 (m, 2H), 7.54 (d, 1H), 7.76 (d, 1H), 7.83 (m, 2H), 7.92 (m, 1H), 8.10 (d, 1H), 8.31 (s, 1H), 8.46 (d, 1H), 9.35 (s, 1H).

Example 61

***N*-Cyclopropyl-4-methyl-3-[4-oxo-6-(2-piperidin-1-ylethoxy)quinazolin-3(4*H*)-yl]benzamide bismethanesulfonate salt**

Using an analogous procedure to that described in Example 45, two equivalents of 1N methanesulfonic acid in ethyl acetate was reacted *N*-cyclopropyl-4-methyl-3-[4-oxo-6-(2-piperidin-1-ylethoxy)quinazolin-3(4*H*)-yl]benzamide to gave the title compound; NMR Spectrum: ($DMSOd_6$) 0.57 (m, 2H), 0.71 (m, 2H), 1.56 (s, 2H), 1.76 (s, 4H), 2.14 (s, 3H),

2.32 (s, 3H), 2.86 (m, 1H), 3.09 (m, 2H), 3.31 (m, 4H), 4.44 (s, 2H), 7.56 (m, 2H), 7.67 (d, 1H), 7.78 (d, 1H), 7.85 (s, 1H), 7.91 (d, 1H), 8.22 (s, 1H), 8.45 (d, 1H).

Example 62

***N*-Cyclopropyl-3-[6-(4-isopropylpiperazin-1-yl)-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide 4-toluenesulfonate salt**

Using an analogous procedure to that described in Example 45, a 0.1N solution of 4-toluenesulfonic acid in ethyl acetate was reacted *N*-cyclopropyl-3-[6-(4-isopropylpiperazin-1-yl)-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide to gave the title compound; NMR Spectrum: (DMSOd_6) 0.57 (m, 2H), 0.71 (m, 2H), 1.32 (d, 6H), 2.14 (s, 3H), 2.29 (s, 3H), 2.86 (m, 1H), 3.11 (m, 2H), 3.22 (m, 2H), 3.53 - 3.63 (m, 3H), 4.09 (m, 2H), 7.11 (d, 2H), 7.49 (d, 2H), 7.54 (d, 1H), 7.58 (s, 1H), 7.72 (m, 2H), 7.83 (d, 1H), 7.91 (m, 1H), 8.17 (s, 1H), 8.45 (d, 1H), 9.31 (s, 1H).

Example 63

***N*-Cyclopropyl-4-methyl-3-[6-(4-methylpiperazin-1-yl)-4-oxoquinazolin-3(4H)-yl]benzamide 4-toluenesulfonate salt**

Using an analogous procedure to that described in Example 45, a 0.1N solution of 4-toluenesulfonic acid in ethyl acetate was reacted with *N*-cyclopropyl-4-methyl-3-[6-(4-methylpiperazin-1-yl)-4-oxoquinazolin-3(4H)-yl]benzamide to gave the title compound; NMR Spectrum: (DMSOd_6) 0.56 (m, 2H), 0.70 (m, 2H), 2.13 (s, 3H), 2.29 (s, 3H), 2.85 (m, 1H), 2.89 (s, 3H), 3.08 (m, 2H), 3.20 (m, 2H), 3.56 (m, 2H), 4.04 (m, 2H), 7.12 (d, 2H), 7.48 (d, 2H), 7.52 - 7.59 (m, 2H), 7.71 (m, 2H), 7.83 (d, 1H), 7.91 (m, 1H), 8.16 (s, 1H), 8.49 (d, 1H), 9.64 (s, 1H).

Example 64

***N*-Cyclopropyl-3-[6-{[(3*S*)-1-isopropylpyrrolidin-3-yl]oxy}-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide 4-toluenesulfonate salt**

Using an analogous procedure to that described in Example 45, a 0.1N solution of 4-toluenesulfonic acid in ethyl acetate was reacted *N*-cyclopropyl-3-[6-{[(3*S*)-1-isopropylpyrrolidin-3-yl]oxy}-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide to gave the title compound; NMR Spectrum: (DMSOd_6) 0.57 (m, 2H), 0.70 (m, 2H), 1.29 (m, 6H), 2.15 (s, 3H), 2.29 (m, 4H), 2.86 (m, 1H), 3.30 (m, 2H), 3.51 (m, 2H), 3.71 (m, 2H), 5.38 (m, 1H), 7.12 (d, 2H), 7.49 (d, 2H), 7.55 (m, 2H), 7.64 (d, 1H), 7.80 (d, 1H), 7.84 (m, 1H), 7.92 (m, 1H), 8.25 (s, 1H), 8.45 (d, 1H), 9.88 (d, 1H).

Example 65

***N*-Cyclopropyl-3-[6-{[2-(dimethylamino)ethyl]thio}-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide 4-toluenesulfonate salt**

Using an analogous procedure to that described in Example 45, a 0.1N solution of 4-toluenesulfonic acid in ethyl acetate was reacted *N*-cyclopropyl-3-[6-{[2-(dimethylamino)ethyl]thio}-4-oxoquinazolin-3(4*H*)-yl]-4-methylbenzamide to gave the title compound; NMR Spectrum: ($DMSOd_6$) 0.57 (m, 2H), 0.71 (m, 2H), 2.15 (s, 3H), 2.29 (s, 3H), 2.83 (s, 6H), 2.87 (m, 1H), 3.28 (m, 2H), 3.46 (m, 2H), 7.11 (d, 2H), 7.49 (d, 2H), 7.54 (d, 1H), 7.79 (d, 1H), 7.84 (d, 1H), 7.93 (m, 2H), 8.15 (d, 1H), 8.32 (s, 1H), 8.46 (d, 1H), 9.45 (s, 1H).

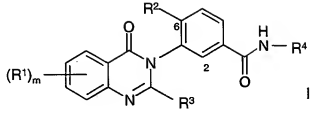
Example 66

***N*-Cyclopropyl-4-methyl-3-[4-oxo-6-(2-piperidin-1-ylethoxy)quinazolin-3(4*H*)-yl]benzamide 4-toluenesulfonate salt**

Using an analogous procedure to that described in Example 45, a 0.1N solution of 4-toluenesulfonic acid in ethyl acetate was *N*-cyclopropyl-4-methyl-3-[4-oxo-6-(2-piperidin-1-ylethoxy)quinazolin-3(4*H*)-yl]benzamide to gave the title compound; NMR Spectrum: ($DMSOd_6$) 0.57 (m, 2H), 0.71 (m, 2H), 1.41 (m, 1H), 1.71 (m, 3H), 1.84 (m, 2H), 2.14 (s, 3H), 2.29 (s, 3H), 2.87 (m, 1H), 3.05 (m, 2H), 3.56 (m, 4H), 4.51 (m, 2H), 7.11 (d, 2H), 7.49 (d, 2H), 7.56 (m, 2H), 7.69 (d, 1H), 7.79 (d, 1H), 7.85 (s, 1H), 7.92 (m, 1H), 8.24 (s, 1H), 8.46 (d, 1H), 9.27 (s, 1H).

Claims

1. A compound of the Formula I



I

wherein m is 0, 1 or 2;

R^1 is halogeno, hydroxy, cyano, trifluoromethyl, trifluoromethoxy, (1-6C)alkyl, (1-6C)alkoxy, (2-6C)alkenyl, (2-6C)alkynyl, (2-6C)alkanoyl, (1-6C)alkylthio, (1-6C)alkylsulphinyl, (1-6C)alkylsulphonyl, hydroxy-(2-6C)alkoxy, amino-(2-6C)alkoxy, cyano-(2-6C)alkoxy, (1-6C)alkylamino-(2-6C)alkoxy, di-[(1-6C)alkyl]amino-(2-6C)alkoxy, (1-6C)alkoxy-(2-6C)alkoxy, carbamoyl-(1-6C)alkoxy, N-(1-6C)alkylcarbamoyl-(1-6C)alkoxy, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl, di[(1-6C)alkyl]amino-(1-6C)alkyl, carbamoyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl-(1-6C)alkyl, hydroxy-(2-6C)alkylamino, cyano-(2-6C)alkylamino, halogeno-(2-6C)alkylamino, amino-(2-6C)alkylamino, (1-6C)alkoxy-(2-6C)alkylamino, (1-6C)alkylamino-(2-6C)alkylamino, di-[(1-6C)alkyl]amino-(2-6C)alkylamino, heteroaryl, heteroaryl-(1-6C)alkyl, heteroaryloxy, heteroaryl-(1-6C)alkoxy, heteroarylamino, heterocyclyl, heterocyclyl-(1-6C)alkyl, heterocyclyloxy, heterocyclyl-(1-6C)alkoxy and heterocyclylamino,

and wherein any aryl, heteroaryl or heterocyclyl group in a R^1 substituent may optionally bear 1 or 2 substituents selected from hydroxy, halogeno, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (3-6C)cycloalkyl, (3-6C)cycloalkyl-(1-6C)alkyl, (3-6C)cycloalkyl-(1-6C)alkoxy, (1-6C)alkoxy, carboxy, (1-6C)alkoxycarbonyl, (1-6C)alkoxycarbonyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, carboxy-(1-6C)alkyl, amino-(1-6C)alkyl, (1-6C)alkylamino-(1-6C)alkyl and di-[(1-6C)alkyl]amino-(1-6C)alkyl,

and wherein any of the R^1 substituents defined hereinbefore which comprises a CH_2 group which is attached to 2 carbon atoms or a CH_3 group which is attached to a carbon or nitrogen atom may optionally bear on each said CH_2 or CH_3 group one or more substituents selected

from halogeno, hydroxy, amino, trifluoromethyl, trifluoromethoxy, oxo, carboxy, carbamoyl, acetamido, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (3-6C)cycloalkyl, (3-6C)cycloalkoxy, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, halogeno-(1-6C)alkyl, (1-6C)alkoxy-(2-6C)alkoxy, (1-6C)alkoxycarbonyl, carbamoyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (1-6C)sulphonyl, (1-6C)sulphamoyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl and heterocyclyloxy, and wherein any heterocyclyl group in a R^1 substituent may optionally bear 1 or 2 oxo or thioxo substituents;

R^2 is halogeno, trifluoromethyl or (1-6C)alkyl;

R^3 is hydrogen, halogeno or (1-6C)alkyl; and

R^4 is (3-6C)cycloalkyl, and R^4 may be optionally substituted by one or more substituents selected from halogeno, hydroxy, amino, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino;

or a pharmaceutically-acceptable salt thereof.

2. A compound according to claim 1 wherein R^1 is halogeno, hydroxy, cyano, trifluoromethyl, trifluoromethoxy, (1-6C)alkyl, (1-6C)alkoxy, (2-6C)alkenyl, (2-6C)alkynyl, (2-6C)alkanoyl, (1-6C)alkylthio, (1-6C)alkylsulphonyl, hydroxy-(2-6C)alkoxy, amino-(2-6C)alkoxy, cyano-(2-6C)alkoxy,(1-6C)alkylamino-(2-6C)alkoxy, di-[(1-6C)alkyl]amino-(2-6C)alkoxy, (1-6C)alkoxy-(2-6C)alkoxy, di[(1-6C)alkyl]amino-(1-6C)alkyl, carbamoyl-(1-6C)alkyl, heteroaryl-(1-6C)alkyl, heteroaryl-(1-6C)alkoxy, heterocyclyl, heterocyclyl-(1-6C)alkyl, heterocyclyloxy and heterocyclyl-(1-6C)alkoxy, and wherein any heteroaryl or heterocyclyl group in a R^1 substituent may optionally bear 1 or 2 substituents selected from hydroxy, halogeno, (1-6C)alkyl, (3-6C)cycloalkyl-(1-6C)alkyl, (3-6C)cycloalkyl-(1-6C)alkoxy, (1-6C)alkoxy, (1-6C)alkoxycarbonyl, (1-6C)alkoxycarbonyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl, and wherein any of the R^1 substituents defined hereinbefore which comprises a CH_2 group which is attached to 2 carbon atoms or a CH_3 group which is attached to a carbon or nitrogen atom may optionally bear on each said CH_2 or CH_3 group one or more substituents selected from halogeno, hydroxy, trifluoromethyl, oxo (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl,

(3-6C)cycloalkyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, halogeno-(1-6C)alkyl, (1-6C)alkoxycarbonyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl and heterocyclyloxy, and wherein any heterocyclyl group in a R^1 substituent may optionally bear 1 or 2 oxo or thioxo substituents;or a pharmaceutically-acceptable salt thereof.

3. A compound according to claim 1 or claim 2 wherein R^1 is halogeno, hydroxy, (1-6C)alkoxy, (2-6C)alkenyl, (2-6C)alkynyl, (2-6C)alkanoyl, (1-6C)alkylthio, (1-6C)alkylsulphonyl, amino-(2-6C)alkoxy, (1-6C)alkylamino-(2-6C)alkoxy, di-[(1-6C)alkyl]amino-(2-6C)alkoxy, di[(1-6C)alkyl]amino-(1-6C)alkyl, carbamoyl-(1-6C)alkyl, heteroaryl-(1-6C)alkyl, heterocyclyl, heterocyclyloxy and heterocyclyl-(1-6C)alkoxy,
and wherein any heteroaryl or heterocyclyl group in a R^1 substituent may optionally bear 1 or 2 substituents selected from hydroxy, halogeno, (1-6C)alkyl, (3-6C)cycloalkyl-(1-6C)alkyl, (3-6C)cycloalkyl-(1-6C)alkoxy, (1-6C)alkoxy, (1-6C)alkoxycarbonyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl,
and wherein any of the R^1 substituents defined hereinbefore which comprises a CH_2 group which is attached to 2 carbon atoms or a CH_3 group which is attached to a carbon or nitrogen atom may optionally bear on each said CH_2 or CH_3 group one or more substituents selected from halogeno, hydroxy, trifluoromethyl, (1-6C)alkyl, (3-6C)cycloalkyl, (1-6C)alkoxy, di-[(1-6C)alkyl]amino, (1-6C)alkoxy-(1-6C)alkyl, (1-6C)alkoxycarbonyl, heteroaryl-(1-6C)alkyl, heterocyclyl and heterocyclyloxy;or a pharmaceutically-acceptable salt thereof.

4. A compound according to claim 1 wherein m is 1 or 2; or a pharmaceutically-acceptable salt thereof.

5. A compound according to claim 1 wherein R^2 is (1-6C)alkyl; or a pharmaceutically-acceptable salt thereof.

6. A compound according to claim 1 or claim 5 wherein R^2 is methyl; or a pharmaceutically-acceptable salt thereof.

7. A compound according to claim 1 wherein R^3 is hydrogen; or a pharmaceutically-acceptable salt thereof.

8. A compound according to claim 1 wherein R^4 is cyclopropyl or cyclobutyl, and R^4 may be optionally substituted by one or more substituents selected from halogeno, hydroxy, amino, (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (1-6C)alkoxy, (1-6C)alkylamino and di-[(1-6C)alkyl]amino; or a pharmaceutically-acceptable salt thereof.

9. A compound according to claim 1 wherein R^4 is cyclopropyl and may be optionally substituted by one or more substituents selected from fluoro, chloro, hydroxy, methyl, ethyl, and methoxy; or a pharmaceutically-acceptable salt thereof.

10. A compound according to claim 1 wherein R^4 is cyclopropyl or cyclobutyl; or a pharmaceutically-acceptable salt thereof.

11. A compound according to claim 1 wherein m is 1;

R^1 is halogeno, hydroxy, cyano, trifluoromethyl, trifluoromethoxy, (1-6C)alkyl, (1-6C)alkoxy, (2-6C)alkenyl, (2-6C)alkynyl, (2-6C)alkanoyl, (1-6C)alkylthio, (1-6C)alkylsulphonyl, hydroxy-(2-6C)alkoxy, amino-(2-6C)alkoxy, cyano-(2-6C)alkoxy, (1-6C)alkylamino-(2-6C)alkoxy, di-[(1-6C)alkyl]amino-(2-6C)alkoxy, (1-6C)alkoxy-(2-6C)alkoxy, di[(1-6C)alkyl]amino-(1-6C)alkyl, carbamoyl-(1-6C)alkyl, heteroaryl-(1-6C)alkyl, heteroaryl-(1-6C)alkoxy, heterocyclyl, heterocyclyl-(1-6C)alkyl, heterocyclyloxy and heterocyclyl-(1-6C)alkoxy,

and wherein any heteroaryl or heterocyclyl group in a R^1 substituent may optionally bear 1 or 2 substituents selected from hydroxy, halogeno, (1-6C)alkyl, (3-6C)cycloalkyl-(1-6C)alkyl, (3-6C)cycloalkyl-(1-6C)alkoxy, (1-6C)alkoxy, (1-6C)alkoxycarbonyl, (1-6C)alkoxycarbonyl-(1-6C)alkyl, N-(1-6C)alkylcarbamoyl, N,N-di-[(1-6C)alkyl]carbamoyl, (2-6C)alkanoyl, amino, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, halogeno-(1-6C)alkyl, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, cyano-(1-6C)alkyl,

and wherein any of the R^1 substituents defined hereinbefore which comprises a CH_2 group which is attached to 2 carbon atoms or a CH_3 group which is attached to a carbon or nitrogen

atom may optionally bear on each said CH_2 or CH_3 group one or more substituents selected from halogeno, hydroxy, trifluoromethyl, oxo (1-6C)alkyl, (2-6C)alkenyl, (2-6C)alkynyl, (3-6C)cycloalkyl, (1-6C)alkoxy, (1-6C)alkylamino, di-[(1-6C)alkyl]amino, hydroxy-(1-6C)alkyl, (1-6C)alkoxy-(1-6C)alkyl, halogeno-(1-6C)alkyl, (1-6C)alkoxycarbonyl, heteroaryl, heteroaryl-(1-6C)alkyl, heterocyclyl and heterocyclyloxy, and wherein any heterocyclyl group in a R^1 substituent may optionally bear 1 or 2 oxo or thioxo substituents;

R^2 is trifluoromethyl or methyl;

R^3 is hydrogen;

R^4 is cyclopropyl or cyclobutyl and may be optionally substituted by one or more substituents selected from fluoro, chloro, hydroxy, methyl, ethyl, and methoxy; or a pharmaceutically-acceptable salt thereof.

12. A compound according to claim 1 wherein m is 1;

R^1 is fluoro, chloro, bromo, iodo, hydroxy, methoxy, ethoxy, propoxy, acetyl, methylthio, ethylthio, methylsulphonyl, ethylsulphonyl, 2-aminoethoxy, 2-amino-1-methylethoxy, 3-aminopropoxy, 2-amino-2-methylpropoxy, 2-methylaminoethoxy, 2-methylamino-1-methylethoxy, 3-ethylaminopropoxy, 2-dimethylaminoethoxy, 2-diethylaminoethoxy, 2-dimethylaminopropoxy, 2-dimethylamino- 2-methylethoxy, 3-dimethylaminopropoxy, dimethylaminomethyl, diethylaminomethyl, 1-dimethylaminoethyl, 2-dimethylaminoethyl, 3-dimethylaminopropyl., carbamoylmethyl, 1-carbamoylethyl, 2-carbamoylethyl, 3-carbamoylpropyl, heteroarylmethyl, heteroarylethyl, heterocyclyl, heterocyclyloxy, heterocyclylmethoxy and 2-heterocyclylethoxy, and wherein any heteroaryl or heterocyclyl group in a R^1 substituent may optionally bear 1 or 2 substituents selected from hydroxy, fluoro, chloro, bromo, iodo, methyl, ethyl, propyl, isopropyl, cyclobutylmethyl, cyclopropylmethyl, cyclobutylmethoxy, cyclopropylmethoxy, acetyl, methoxy, ethoxy, propoxy, methoxycarbonylmethyl, ethoxycarbonylmethyl, tert-butoxycarbonylmethyl, 1-methoxycarbonylethyl, 1-ethoxycarbonylethyl, 2-methoxycarbonylethyl, 2-ethoxycarbonylethyl, 3-methoxycarbonylpropyl, 3-ethoxycarbonylpropyl, N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl, N,N-dimethylcarbamoyl, N-ethyl-N-methylcarbamoyl, N,N-diethylcarbamoyl, fluoromethyl, chloromethyl, bromomethyl, difluoromethyl, dichloromethyl, dibromomethyl, 2-fluoroethyl,

2-chloroethyl, 2-bromoethyl, hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl, 3-hydroxypropyl, methoxymethyl, ethoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 2-ethoxyethyl and 3-methoxypropyl, cyanomethyl, 2-cyanoethyl, 1-cyanoethyl, 3-cyanopropyl,

and wherein any of the R^1 substituents defined hereinbefore which comprises a CH_2 group which is attached to 2 carbon atoms or a CH_3 group which is attached to a carbon or nitrogen atom may optionally bear on each said CH_2 or CH_3 group one or more substituents selected from fluoro, chloro, bromo, iodo, hydroxy, trifluoromethyl, methyl, ethyl, propyl, isopropyl, tert-butyl, cyclopropyl, cyclobutyl, cyclopentyl, methoxy, ethoxy, propoxy, isopropoxy, tert-butoxy, dimethylamino, diethylamino, N-ethyl-N-methylamino, methoxymethyl, ethoxymethyl, 1-methoxyethyl, 2-methoxyethyl, 2-ethoxyethyl, 3-methoxypropyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl,tert-butoxycarbonyl, heteroarylmethyl, heteroarylethyl, heterocyclyl and heterocyclyloxy

R^2 is methyl;

R^3 is hydrogen;

R^4 is cyclopropyl or cyclobutyl and may be optionally substituted by methyl; or a pharmaceutically-acceptable salt thereof.

13. A compound according to claim 1 selected from:-

N-cyclopropyl-4-methyl-3-[6-(4-methylpiperazin-1-yl)-4-oxoquinazolin-3(4H)-yl]benzamide,
N-cyclobutyl-4-methyl-3-[6-(4-methylpiperazin-1-yl)-4-oxoquinazolin-3(4H)-yl]benzamide,
N-cyclopropyl-4-methyl-3-[4-oxo-6-(piperidin-4-yloxy)quinazolin-3(4H)-yl]benzamide,
N-cyclopropyl-3-[6-({1-(cyclopropylmethyl)piperidin-4-yl]oxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide,
N-cyclopropyl-3-[6-(1,4-diazepan-1-yl)-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide,
N-cyclopropyl-4-methyl-3-(4-oxo-6-piperazin-1-ylquinazolin-3(4H)-yl)benzamide,
N-cyclopropyl-4-methyl-3-[6-(4-methyl-1,4-diazepan-1-yl)-4-oxoquinazoline-3(4H)-yl]benzamide,
N-cyclopropyl-4-methyl-3-[6-(4-ethylpiperazin-1-yl)-4-oxoquinazoline-3(4H)-yl]benzamide,
N-cyclopropyl-4-methyl-3-[6-(4-isopropylpiperazin-1-yl)-4-oxoquinazoline-3(4H)-yl]benzamide,
N-cyclopropyl-4-methyl-3-[6-[(3S)-3-methylpiperazin-1-yl]-4-oxoquinazoline-3(4H)-

yl]benzamide,

N-cyclopropyl-4-methyl-3-[6-[(3R)-3-methylpiperazin-1-yl]-4-oxoquinazoline-3(4H)-yl]benzamide,

N-cyclopropyl-4-methyl-3-[6-[4-(2-hydroxyethyl) piperazin-1-yl]-4-oxoquinazoline-3(4H)-yl]benzamide,

N-cyclopropyl-4-methyl-3-[4-oxo-6-(4-propylpiperazin-1-yl)quinazolin-3(4H)-yl]benzamide,

N-cyclopropyl-4-methyl-3-[4-oxo-6-(4-propyl-1,4-diazepan-1-yl)quinazolin-3(4H)-yl]benzamide,

N-cyclopropyl-4-trifluoromethyl-3-[6-(4-methylpiperazin-1-yl)-4-oxoquinazolin-3(4H)-yl]benzamide,

N-cyclopropyl-4-methyl-3-[6-(4-[tert-butylacetyl]piperazin-1-yl)-4-oxoquinazoline-3(4H)-yl]benzamide,

N-cyclopropyl-4-methyl-3-[6-[(3S)-3,4-dimethylpiperazin-1-yl)]-4-oxoquinazoline-3(4H)-yl]benzamide,

N-cyclopropyl-4-methyl-3-[6-[(3R)-3,4-dimethylpiperazin-1-yl]-4-oxoquinazoline-3(4H)-yl]benzamide,

N-cyclopentyl-4-methyl-3-[6-(4-methylpiperazin-1-yl)-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-3-[6-[(3-hydroxy-2,2-dimethylpropyl)amino]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[2-methyl-6-(4-methyl-1,4-diazepan-1-yl)-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-3-[6-[4-(cyclopropylmethyl)-1,4-diazepan-1-yl]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-(4-ethyl-1,4-diazepan-1-yl)-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-[4-(2-methoxyethyl)-1,4-diazepan-1-yl]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

3-[6-[4-(2-amino-2-oxoethyl)-1,4-diazepan-1-yl]-4-oxoquinazolin-3(4H)-yl]-N-cyclopropyl-4-methylbenzamide;

[4-(3-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4-oxo-3,4-dihydroquinazolin-6-yl)piperazin-1-yl]acetic acid;

N-cyclopropyl-3-[6-[4-(cyclopropylmethyl)piperazin-1-yl]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-[4-(2-ethoxyethyl)piperazin-1-yl]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-2-methyl-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-(7-fluoro-4-oxoquinazolin-3(4H)-yl)-4-methylbenzamide;

N-cyclopropyl-3-[6-(2,3-dihydroxy-2-methylpropoxy)-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-(6-isobutoxy-4-oxoquinazolin-3(4H)-yl)-4-methylbenzamide;

N-cyclopropyl-3-[6-(2-hydroxy-2-methyl-3-pyrrolidin-1-ylpropoxy)-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-(6-morpholin-4-yl-4-oxoquinazolin-3(4H)-yl)benzamide;

N-cyclopropyl-4-methyl-3-(4-oxo-6-thiomorpholin-4-ylquinazolin-3(4H)-yl)benzamide;

N-cyclopropyl-3-[6-(4-hydroxypiperidin-1-yl)-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-(3-hydroxyazetidin-1-yl)-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[6-(4-methyl-4-oxidopiperazin-1-yl)-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-[6-[4-(methylsulfonyl)piperazin-1-yl]-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-3-[6-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[6-(4-methylpiperidin-1-yl)-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-(4-oxo-6-piperidin-1-ylquinazolin-3(4H)-yl)benzamide;

4-methyl-N-(1-methylcyclopropyl)-3-[6-(4-methylpiperazin-1-yl)-4-oxoquinazolin-3(4H)-yl]benzamide;

3-[6-[4-(cyanomethyl)piperazin-1-yl]-4-oxoquinazolin-3(4H)-yl]-N-cyclopropyl-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[4-oxo-6-(4-prop-2-yn-1-ylpiperazin-1-yl)quinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-(4-oxoquinazolin-3(4H)-yl)benzamide;

3-[6-(4-acetylpiperazin-1-yl)-4-oxoquinazolin-3(4H)-yl]-N-cyclopropyl-4-methylbenzamide;

3-[6-(4-cyclobutylpiperazin-1-yl)-4-oxoquinazolin-3(4H)-yl]-N-cyclopropyl-4-methylbenzamide;

N-cyclopropyl-3-(6-iodo-4-oxoquinazolin-3(4H)-yl)-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[6-[(1-methylpiperidin-4-yl)oxy]-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-3-(6-methoxy-4-oxoquinazolin-3(4H)-yl)-4-methylbenzamide;

3-[6-(4-isopropylpiperazin-1-yl)-4-oxoquinazolin-3(4H)-yl]-4-methyl-N-(1-methylcyclopropyl)benzamide;

N-cyclobutyl-3-[6-(4-isopropylpiperazin-1-yl)-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-[(1-ethylpiperidin-4-yl)oxy]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[7-(4-methylpiperazin-1-yl)-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-3-[6-[(1-isopropylpiperidin-4-yl)oxy]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[4-oxo-6-[4-(1,3-thiazol-4-ylmethyl)piperazin-1-yl]quinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-[6-{4-[(5-methylisoxazol-3-yl)methyl]piperazin-1-yl}-4-oxoquinazolin-3(4H)-yl]benzamide;

tert-butyl 3-[(3-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4-oxo-3,4-dihydroquinazolin-6-yl)oxy]pyrrolidine-1-carboxylate;

N-cyclopropyl-4-methyl-3-[4-oxo-6-(pyrrolidin-3-yloxy)quinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-[4-oxo-6-(pyridin-2-ylmethoxy)quinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-3-[6-[4-(2-fluoroethyl)piperazin-1-yl]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-[4-(2,2-difluoroethyl)piperazin-1-yl]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[4-oxo-6-{4-[2-(tetrahydro-2H-pyran-2-yloxy)ethyl]piperazin-1-yl}quinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-[6-[(1-methylpyrrolidin-3-yl)oxy]-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-3-[6-[(1-ethylpyrrolidin-3-yl)oxy]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-{[1-(cyclopropylmethyl)pyrrolidin-3-yl]oxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-{[1-(2-fluoroethyl)piperidin-4-yl]oxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-{[1-(2-methoxyethyl)piperidin-4-yl]oxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-[2-(dimethylamino)ethoxy]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-[(1-cyclopropylpiperidin-4-yl)oxy]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-[(3R)-4-ethyl-3-methylpiperazin-1-yl]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[7-fluoro-6-(4-methylpiperazin-1-yl)-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-[(3R)-4-isopropyl-3-methylpiperazin-1-yl]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-[(3R)-4-(cyclopropylmethyl)-3-methylpiperazin-1-yl]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[4-oxo-6-(2-pyrrolidin-1-ylethoxy)quinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-[6-(2-morpholin-4-ylethoxy)-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-[4-oxo-6-(2-piperidin-1-ylethoxy)quinazolin-3(4H)-yl]benzamide;

3-[6-(2-azetidin-1-ylethoxy)-4-oxoquinazolin-3(4H)-yl]-N-cyclopropyl-4-methylbenzamide;

tert-butyl 5-(3-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4-oxo-3,4-dihydroquinazolin-6-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate;

N-cyclopropyl-3-[6-[3-(dimethylamino)propoxy]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-[(1-isopropylpyrrolidin-3-yl)oxy]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[6-(5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl)-4-oxoquinazolin-3(4*H*)-yl]benzamide;

N-cyclopropyl-3-(6-hydroxy-4-oxoquinazolin-3(4H)-yl)-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[4-oxo-6-(1,2,3,6-tetrahydropyridin-4-yl)quinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-3-[6-[2-(4-isopropylpiperazin-1-yl)ethoxy]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-[2-(4,4-difluoropiperidin-1-yl)ethoxy]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-{2-[(3R)-3-fluoropyrrolidin-1-yl]ethoxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[4-oxo-6-[(3S)-pyrrolidin-3-yloxy]quinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-[6-[2-(1,4-oxazepan-4-yl)ethoxy]-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-[6-{2-[methyl(pyridin-2-ylmethyl)amino]ethoxy}-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-[4-oxo-6-[4-(2,2,2-trifluoro-1-methylethyl)piperazin-1-yl]quinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-3-[6-{2-[(2-methoxyethyl)(methyl)amino]ethoxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-(4-oxopyrido[3,4-d]pyrimidin-3(4H)-yl)benzamide;

N-cyclopropyl-4-methyl-3-[6-{[(3S)-1-methylpyrrolidin-3-yl]oxy}-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-3-[6-{[(3S)-1-ethylpyrrolidin-3-yl]oxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-{[(3S)-1-(cyclopropylmethyl)pyrrolidin-3-yl]oxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-{[(3S)-1-isopropylpyrrolidin-3-yl]oxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-(4-oxopyrido[2,3-d]pyrimidin-3(4H)-yl)benzamide;

N-cyclopropyl-4-methyl-3-[4-oxo-6-[(3R)-pyrrolidin-3-yloxy]quinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-[4-oxo-6-(3-piperidin-1-ylpropoxy)quinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-[4-oxo-6-[2-(1H-pyrrol-1-yl)ethoxy]quinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-[4-oxo-6-(3-pyrrolidin-1-ylpropoxy)quinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-3-[6-[2-(dimethylamino)-2-methylpropoxy]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[4-oxo-6-[3-(1H-pyrrol-1-yl)propoxy]quinazolin-3(4H)-yl]benzamide;

3-[6-(2-aminoethoxy)-4-oxoquinazolin-3(4H)-yl]-N-cyclopropyl-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[6-{[(3R)-1-methylpyrrolidin-3-yl]oxy}-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-3-[6-{[(3R)-1-ethylpyrrolidin-3-yl]oxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-{[(3R)-1-(cyclopropylmethyl)pyrrolidin-3-yl]oxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-{[(3R)-1-isopropylpyrrolidin-3-yl]oxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-[2-(dimethylamino)-2-oxoethoxy]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[6-{2-[(methylsulfonyl)amino]ethoxy}-4-oxoquinazolin-3(4H)-yl]benzamide;

3-[6-[2-(acetylamino)ethoxy]-4-oxoquinazolin-3(4H)-yl]-N-cyclopropyl-4-methylbenzamide;

N-cyclopropyl-3-(7-methoxy-4-oxoquinazolin-3(4H)-yl)-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[6-[3-(4-methylpiperazin-1-yl)propoxy]-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-[6-[(1-methylpiperidin-3-yl)methoxy]-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-3-[6-[2-(1H-imidazol-1-yl)ethoxy]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[4-oxo-6-[2-(2-oxoimidazolidin-1-yl)ethoxy]quinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-[6-[(1-methylpiperidin-2-yl)methoxy]-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-[6-[(1-methyl-1H-imidazol-2-yl)methoxy]-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-3-[6-{[2-(dimethylamino)ethyl]thio}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[4-oxo-6-(2-thiomorpholin-4-ylethoxy)quinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-3-[6-[2-(4-hydroxypiperidin-1-yl)ethoxy]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

3-[6-{2-[(cyclobutylmethyl)(methyl)amino]ethoxy}-4-oxoquinazolin-3(4H)-yl]-N-cyclopropyl-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[6-(2-{methyl[2-(methylsulfonyl)ethyl]amino}ethoxy)-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-[6-(2-{methyl[(1-methyl-1H-pyrazol-4-yl)methyl]amino}ethoxy)-4-oxoquinazolin-3(4H)-yl]benzamide;

methyl (2E)-3-(3-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-4-oxo-3,4-dihydroquinazolin-6-yl)acrylate;

N-cyclopropyl-3-[6-[3-(dimethylamino)prop-1-yn-1-yl]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-[3-(dimethylamino)propyl]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[6-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-[6-(1-methylpiperidin-4-yl)-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-3-[7-[3-(dimethylamino)propoxy]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[7-(2-morpholin-4-ylethoxy)-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-3-[6-({1-(2-hydroxy-2-methylpropyl)piperidin-4-yl]oxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-({1-[(2S)-2-hydroxypropyl]piperidin-4-yl}oxy)-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-({1-[(2R)-2-hydroxypropyl]piperidin-4-yl}oxy)-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[4-oxo-6-[(2S)-pyrrolidin-2-ylmethoxy]quinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-[6-{[(2S)-1-methylpyrrolidin-2-yl]methoxy}-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-3-[6-{[1-(2-hydroxyethyl)piperidin-4-yl]oxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-{2-[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]ethoxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-{2-[(2S)-2-(methoxymethyl)pyrrolidin-1-yl]ethoxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-{2-[isopropyl(methyl)amino]ethoxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-{2-[isopropyl(2-methoxyethyl)amino]ethoxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

3-[6-[2-(tert-butylamino)ethoxy]-4-oxoquinazolin-3(4H)-yl]-N-cyclopropyl-4-methylbenzamide;

N-cyclopropyl-3-[6-[3-(dimethylamino)-2-methylpropoxy]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[6-[(4-methylmorpholin-2-yl)methoxy]-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-[8-(4-methylpiperazin-1-yl)-4-oxoquinazolin-3(4H)-yl]benzamide;

3-[6-[2-(dimethylamino)ethoxy]-4-oxoquinazolin-3(4H)-yl]-4-methyl-N-(1-methylcyclopropyl)benzamide;

4-methyl-N-(1-methylcyclopropyl)-3-[4-oxo-6-(2-piperidin-1-ylethoxy)quinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-3-(8-methoxy-4-oxoquinazolin-3(4H)-yl)-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[4-oxo-6-[(2R)-pyrrolidin-2-ylmethoxy]quinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-4-methyl-3-[6-{[(2R)-1-methylpyrrolidin-2-yl]methoxy}-4-oxoquinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-3-[6-{[(2S)-1-glycoloylpyrrolidin-2-yl]methoxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-4-methyl-3-[4-oxo-6-(3-thiomorpholin-4-ylpropoxy)quinazolin-3(4H)-yl]benzamide;

N-cyclopropyl-3-[6-{3-[(3R)-3-hydroxypyrrolidin-1-yl]propoxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-[3-(4-hydroxypiperidin-1-yl)propoxy]-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

N-cyclopropyl-3-[6-{3-[(2-methoxyethyl)(methyl)amino]propoxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide;

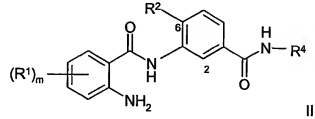
N-cyclopropyl-3-[6-{3-[(3-furylmethyl)(methyl)amino]propoxy}-4-oxoquinazolin-3(4H)-yl]-4-methylbenzamide; and

3-[6-{3-[(cyclobutylmethyl)(methyl)amino]propoxy}-4-oxoquinazolin-3(4H)-yl]-N-cyclopropyl-4-methylbenzamide;

or a pharmaceutically-acceptable salt thereof.

14. A process for preparing a compound of the Formula I according to claim 1, or pharmaceutically-acceptable salt thereof which comprises:-

(a) reacting an N-phenyl-2-aminobenzamide of the Formula II



II

with a carboxylic acid of the Formula III, or a reactive derivative thereof,

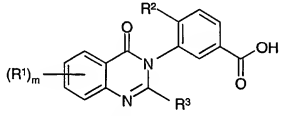
III

wherein variable groups are as defined in claim 1 and wherein any functional group is protected if necessary, and:

(i) removing any protecting groups; and

(ii) optionally forming a pharmaceutically-acceptable salt;

(b) reacting a carboxylic acid of the Formula X or a reactive derivative thereof as defined hereinbefore,



X

with a amine of the Formula VI,

VI

under standard amide bond forming conditions as defined hereinbefore, wherein variable groups are as defined in claim 1 and wherein any functional group is protected if necessary, and:

(i) removing any protecting groups; and

(ii) optionally forming a pharmaceutically-acceptable salt.

15. A pharmaceutical composition for use in the treatment of diseases mediated by cytokines which comprises compound of the Formula I as claimed in any one of claims 1 to 13, or a pharmaceutically-acceptable salt thereof, in association with a pharmaceutically-acceptable diluent or carrier.

16. A compound of the Formula I claimed in any one of claims 1 to 13, or a pharmaceutically-acceptable salt thereof, for use in a method of treatment of the human or animal body by therapy.

17. A method of treating diseases or medical conditions mediated by cytokines which comprises administering to a warm-blooded animal an effective amount of a compound of the Formula I claimed in any one of claims 1 to 13, or a pharmaceutically-acceptable salt thereof.

18. A method of treating a disease or medical condition mediated by cytokines which comprises administering to a warm-blooded animal in need thereof a cytokine inhibiting amount of a compound of the Formula I claimed in any one of claims 1 to 13, or a pharmaceutically-acceptable salt thereof.

19. A method of treating a disease or medical condition mediated by the production or effect of cytokines which comprises administering to a warm-blooded animal in need thereof a cytokine inhibiting amount of a compound of the Formula I claimed in any one of claims 1 to 13, or a pharmaceutically-acceptable salt thereof.

20. A method of treating rheumatoid arthritis, asthma, chronic obstructive pulmonary disease, inflammatory bowel disease, multiple sclerosis, AIDS, septic shock, congestive heart failure, ischaemic heart disease or psoriasis which comprises administering to a warm-blooded animal an effective amount of a compound of the Formula I claimed in any one of claims 1 to 13, or a pharmaceutically-acceptable salt thereof.

21. A compound of the Formula I claimed in any one of claims 1 to 13, or a pharmaceutically-acceptable salt thereof, in the manufacture of a medicament.

22. A compound of the Formula I claimed in any one of claims 1 to 13, or a pharmaceutically-acceptable salt thereof, in the manufacture of a medicament for use in the treatment of medical conditions mediated by cytokines.

23. The use of a compound of the Formula I claimed in any one of claims 1 to 13, or a pharmaceutically-acceptable thereof, in the manufacture of a medicament for use in the treatment of rheumatoid arthritis, asthma, chronic obstructive pulmonary disease, inflammatory bowel disease, multiple sclerosis, AIDS, septic shock, congestive heart failure, ischaemic heart disease or psoriasis.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/GB2004/004474

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D239/91 A61K31/513

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other then minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 00/20402 A (CUMMING JOHN GRAHAM ; ZENECA LTD (GB)) 13 April 2000 (2000-04-13) the whole document	1-23
Y	WO 00/55153 A (BROWN DEARG SUTHERLAND ; ASTRAZENECA AB (SE)) 21 September 2000 (2000-09-21) cited in the application the whole document	1-23

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 January 2005	27/01/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Zellner, A

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; BARAKAT, SABER EL-SAYED ET AL: "Synthesis and hypnotic activity of some new quinazolinone derivatives" XP002313093 retrieved from STN Database accession no. 1995:893816 abstract & SAUDI PHARMACEUTICAL JOURNAL , 3(3), 84-9 CODEN: SPJOEM; ISSN: 1319-0164, 1995,	1-23
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A	WO 02/083143 A (JOHNSON MICHAEL G ; HUANG ALAN XI (US); LIU JIWEN (US); TULARIK INC (U) 24 October 2002 (2002-10-24) the whole document	1-23
A	HANSON G J: "inhibitors of p38 kinase" EXPERT OPINION ON THERAPEUTIC PATENTS, ASHLEY PUBLICATIONS, GB, vol. 7, no. 7, 1997, pages 729-733, XP002086152 ISSN: 1354-3776 cited in the application the whole document	1-23

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2004/004474

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 17-23 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2004/004474

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INTERNATIONAL SEARCH REPORT

In ~ ional Application No
PCT/GB2004/004474

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Form PCT/ISA/210 (patent family annex) (January 2004)